

Androgen Deprivation Therapy with or without Radium-223 dichloride in Patients with Newly  
Diagnosed Metastatic Prostate Cancer with Bone Metastases  
HCRN GU13-170

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to HCRN and keep a record for your files.

\_\_\_\_\_  
Signature of Investigator

\_\_\_\_\_  
Date

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Investigator Title

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Name of Facility

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Location of Facility (City and State)

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Expected IRB Approval Date

Not Submitting to IRB

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**STUDY SYNOPSIS**

<b>TITLE</b>	Androgen Deprivation Therapy with or without Radium-223 dichloride in patients with Newly Diagnosed Metastatic Prostate Cancer with Bone Metastases: HCRN GU13-170
<b>PHASE</b>	Phase II, randomized
<b>OBJECTIVES</b>	<p><b><u>Primary Objectives:</u></b></p> <ol style="list-style-type: none"> <li>1. Determine whether the combination of ADT plus radium-223 dichloride is more effective than ADT alone based upon radiologic progression free survival (rPFS) in subjects with newly diagnosed metastatic prostate cancer with bone metastases.</li> </ol> <p><b><u>Secondary Objective(s):</u></b></p> <ol style="list-style-type: none"> <li>1. Assess safety and toxicity including incidence of skeletal related events (SRE) and secondary neoplasms.</li> <li>2. Estimate the proportion of subjects with PSA <math>\leq</math> 0.2 ng/mL after 7 months of androgen deprivation therapy, the proportion of subjects with PSA <math>\leq</math> 4 ng/mL after 7 months of androgen deprivation therapy, the median time to castration resistance, 2-year PSA progression free survival proportion (PCWG2 criteria) and 2-year overall survival proportion in both arms.</li> <li>3. Determine the proportion of subjects with elevated serum total alkaline phosphatase (ALP) at baseline who normalize their alkaline phosphatase after 12 weeks of therapy, assess time to ALP progression (<math>\geq</math> 25% increase in ALP from baseline/nadir (whichever is lower) and above ULN), association of ALP x in both arms.</li> <li>4. Evaluate change in pain level and analgesic use using the Brief Pain Inventory (BPI short form) and WHO ladder scale, respectively, with therapy.</li> </ol> <p><b><u>Exploratory Correlative Objectives:</u></b></p> <ol style="list-style-type: none"> <li>1. Assess number of circulating tumor cells (CTCs) and gamma H2AX in all subjects (number of subjects = 204)</li> <li>2. Explore the association of bone turnover markers with clinical outcome and change in serum bone turnover markers with therapy in both arms.</li> </ol>
<b>STUDY DESIGN</b>	Newly diagnosed metastatic prostate cancer subjects with bone metastases will be accrued to this stratified randomized 2-arm Phase II trial. Subjects will be randomized 1:2 to ADT or ADT with Radium-223 dichloride respectively. The primary aim of the study is to determine if the addition of Radium-223 dichloride to ADT will improve treatment efficacy in this population. The primary efficacy endpoint is radiographic progression-free survival (rPFS). We expect the control arm with ADT alone to have a 12 month median rPFS. The addition of radium-223 to ADT will target an improvement of 7 months for a median rPFS of 19 months. A total of 140 events are required for at least 90% power to detect Hazard Ratio of 0.632 with a one-sided alpha of 0.1. The study powering is based on assumptions of 19 months median rPFS in the experimental arm and 12 months median rPFS in the control arm. Assuming exponential time to event

	<p>data, a yearly dropout rate of 10% with accrual in 24 months and study duration of 48 months, 204 subjects will provide 90% power with a 10% one-sided type I error. Hypothesis testing for the primary endpoint will be conducted at a one-sided 0.10 significance level using a stratified log-rank test. Randomization of 68 subjects to the ADT arm and 136 subjects to the ADT+R arm will be completed with stratification by extent of disease (&lt;6 skeletal metastases without visceral disease versus <math>\geq 6</math> skeletal metastases or visceral disease) and baseline alkaline phosphatase (normal versus abnormal). If time anticipated for the number of events required for analysis significantly exceeds 48 months, the sponsor may enroll additional subjects to reach required number of events.</p>
<p><b>TOTAL NUMBER OF SUBJECTS</b></p>	<p>Targeted Accrual: 204 subjects over 24 months.</p>
<p><b>ELIGIBILITY CRITERIA</b></p>	<p><b>INCLUSION CRITERIA:</b></p> <ol style="list-style-type: none"> <li>1. Histological or cytological evidence of prostate adenocarcinoma</li> <li>2. Men <math>\geq 18</math> years of age at the time of informed consent</li> <li>3. All subjects must have radiologic or pathologic evidence of <math>\geq 2</math> skeletal lesions with or without pain at baseline on bone scan or axial imaging or with 1 skeletal lesion and bone pain within 28 days prior to the registration.</li> <li>4. All subjects must have a radiographic assessment (chest or abdominal/pelvic CT or MRI) within 28 days prior to registration but do not need to have measurable disease.</li> <li>5. ECOG performance status of 0-2 (3 is allowed if solely due to bone metastases)</li> <li>6. Adequate organ function as below: <ul style="list-style-type: none"> <li>• Absolute neutrophil count (ANC) <math>\geq 1.5</math> K/mm<sup>3</sup></li> <li>• Platelet count <math>\geq 100</math> K/mm<sup>3</sup></li> <li>• Hemoglobin <math>\geq 8.0</math> g/dL (80 g/L) without packed RBC transfusion</li> <li>• Total bilirubin level <math>\leq 2</math> x institutional upper limit of normal (ULN) except subjects with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL</li> <li>• Aspartate aminotransferase (AST) <math>\leq 2.5</math> x ULN</li> <li>• Alanine aminotransferase (ALT) <math>\leq 2.5</math> x ULN</li> <li>• Estimated Creatinine Clearance by Cockcroft-Gault formula <math>\geq 30</math> mL/min</li> </ul> </li> <li>7. Any prior neoadjuvant or adjuvant androgen-deprivation therapy or finasteride must have been discontinued at least 6 months prior to registration.</li> <li>8. Subjects must fall into one of the two populations below: <ul style="list-style-type: none"> <li>• <u>Early Induction Group</u>: Subjects who have started androgen deprivation therapy (luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy with or without an antiandrogen agent) a maximum of 28 days before registration.</li> <li>• <u>Late Induction Group</u>: Subjects who have NOT started androgen deprivation therapy (luteinizing hormone-releasing hormone (LHRH)</li> </ul> </li> </ol>

	<p>agonist or antagonist therapy with or without an antiandrogen agent)</p> <ol style="list-style-type: none"><li>9. All subjects should provide written informed written consent and HIPAA authorization.</li><li>10. Patients with ‘high extent or extensive stage’ of metastases (per CHARTED/E3805) study: visceral metastasis or more than 4 bone metastases including at least 1 non-axial bone metastasis or both) should be considered unsuitable candidates for docetaxel per the treating physician’s clinical judgment, or should have declined docetaxel therapy.</li></ol> <p><b>EXCLUSION CRITERIA:</b></p> <ol style="list-style-type: none"><li>1. History of or active CNS metastases (brain, leptomeningeal or cord compression).</li><li>2. Any neuroendocrine differentiation including small cell component on histology or cytology.</li><li>3. Receiving another investigational agent concomitantly or within the previous 28 days.</li><li>4. Prior or ongoing bisphosphonate or RANKL inhibitor use is not allowed except when used solely for osteoporosis and per guidelines for that indication.</li><li>5. Prior therapy with systemic radiopharmaceuticals including strontium-89, samarium-153, rhenium-186 or rhenium-188 for the treatment of bone metastases.</li><li>6. Prior hemibody external radiation is not allowed. Any external radiation therapy must have been completed at least 14 days prior to registration. Any toxicity from such therapy must have recovered to <math>\leq</math> grade 1 per CTCAE v4 criteria by the time of registration.</li><li>7. No prior malignancy is allowed EXCEPT for non-melanomatous skin cancer or non-muscle invasive bladder cancer or adequately treated Stage I or II cancer (adequacy at discretion of site investigator) from which the subject is currently in complete remission, or any other cancer from which the subject has been disease-free for at least 3 years.</li></ol>
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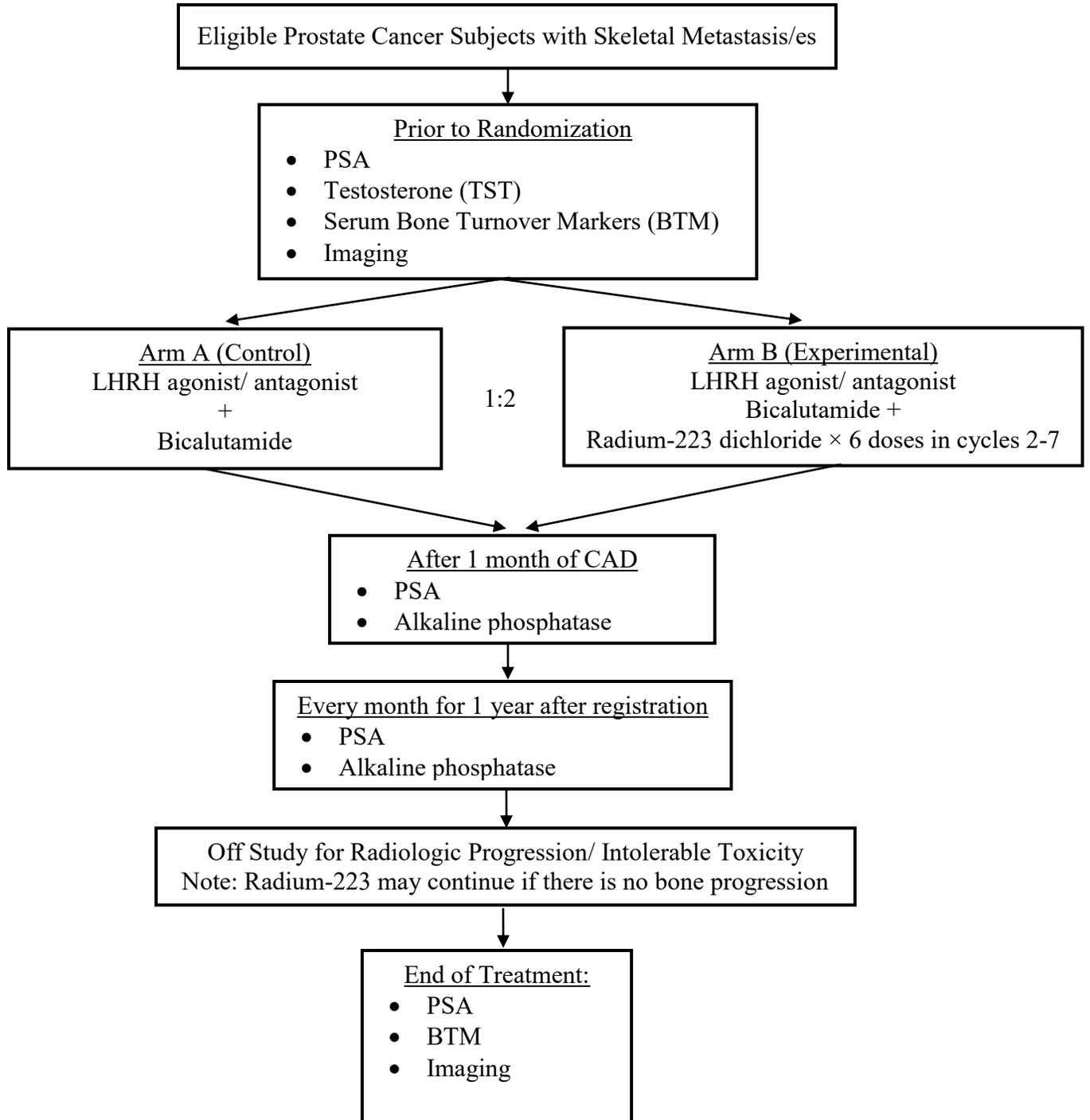
<p><b>OUTCOME MEASURES</b></p>	<p><b>PRIMARY OUTCOME MEASURES:</b> Subjects will be assessed for radiographic progression as described in Section 8. Time to radiographic progression or death, whichever occurs first, will be calculated for each subject.</p> <p><b>SECONDARY OUTCOME MEASURES:</b></p> <ul style="list-style-type: none"> <li>• AE and SAE data, skeletal related events and secondary neoplasms will describe toxicity.</li> <li>• Secondary efficacy measures are time to castration resistance, PSA progression free survival, overall survival, 7-month PSA <math>\leq</math> 0.2 ng/mL, and 7-month PSA <math>\leq</math> 4 ng/mL.</li> <li>• Serum outcomes are ALP normalization among subjects with abnormal ALP at randomization and serum bone markers</li> <li>• Pain outcomes from BPI-SF and physician assigned WHO.</li> </ul>
<p><b>STATISTICAL CONSIDERATIONS</b></p>	<p><b>Primary Analysis</b> Subjects will be assessed for radiographic progression as described in Section 8. Time from first dose of ADT to radiographic progression or death, whichever occurs first, will be calculated for each subject. For subjects who discontinue study treatment due to reasons other than death or investigator assessed progression, every effort will be made to continue tumor assessments on schedule until radiographic progressive disease or subject death. Subjects who do not have radiographic progression or death will be censored at their last measure for radiographic progression. The primary hypothesis test will be conducted at a one-sided 0.1 significance level using a stratified log-rank test. Kaplan-Meier methods will be used to report rPFS graphically by arm including the median rPFS and 12 and 24 month rPFS proportions in the ITT population. The log-rank test without stratification will be used as a sensitivity analysis.</p> <p><b>Secondary analysis</b> Toxicity will be described within each arm by type, maximum grade and frequency among the safety population. The proportion of subjects in each arm with skeletal related events and secondary neoplasms will be reported individually and a mid p-value test will compare the proportions between arms.</p> <p>Time to castration resistance (TTCR), PSA progression free survival (PCWG2 criteria), and Overall Survival (OS) will be reported by arm using Kaplan-Meier methods and tested using the stratified log-rank test. The 2 -year PSA PFS and OS proportions with 90% confidence intervals and median time to castration resistance will be reported using Kaplan-Meier methods. Analyses will be completed on the ITT population.</p> <p>Binomial proportions with 90% binomial confidence intervals of subjects who achieve PSA <math>\leq</math> 0.2 ng/mL at 7 months after treatment initiation will be reported by arm. Similarly, the proportions and associated confidence intervals of subjects who achieve PSA <math>\leq</math> 4 ng/mL at 7 months after treatment initiation will be</p>

	<p>described.</p> <p>We will evaluate the distribution of pre-randomization marker levels (ALP and bone markers) among those who have and have not started ADT prior to randomization. If it appears that the prior initiation of ADT impacts the study entry bone marker levels to a fair extent, then all marker analyses will be conducted stratified by ADT initiation status. Descriptive statistics by arm will report the time to ALP progression among all subjects using Kaplan-Meier methods. ALP and serum bone markers will be reported by arm for each time-point using means or medians and corresponding measures of variability for all subjects with serum. Percentage change in ALP from baseline and changes from baseline in bone markers will be calculated for each later time point and tested between arms using a t-test or Wilcoxon rank test. If there is sufficient data, a mixed model will be used to model each endpoint over time to determine if the changes are different between treatment arms. Exploratory analysis will use separate Cox models with rPFS, PSA PFS, TTCR, and OS as the individual outcomes and treatment group, one marker, and the interaction between treatment and marker as independent covariates to find associations with outcomes. These models can be expanded to include other subject factors to determine if the marker contributes to outcome above subject factors that are known to be associated with the outcome. Similarly, logistic models can be used with 7-month PSA outcomes. The model analyses are considered exploratory for this trial. Thus, they are not powered and will not use multiple comparisons adjustments.</p> <p>Worst pain will be reported from the BPI (SF) at each time point with a mean or median and the associated measure of variability and tested between arms with a t-test or Wilcoxon rank test. Comparisons at the times post-baseline will be compared between treatment arms using a paired test (t-test or Wilcoxon rank test.) WHO will be reported categorically by arm at each time point and tested between arms using the Mantel-Haenszel chi-square test. The change in WHO score from baseline will be calculated and be the outcome in a cumulative logistic model. Treatment arm will be included as an independent covariate to test if the change in pain is different between arms. Each post-baseline measure will be a separate model.</p>
<b>ENROLLMENT PERIOD</b>	Estimated 24 months
<b>TOTAL STUDY DURATION</b>	4 years; 2 years for accrual and 2 years for follow-up

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**SCHEMA**  
**Androgen Deprivation Therapy with or without Radium-223 dichloride  
in Newly Diagnosed Metastatic Prostate Cancer with Bone Metastases: HCRN GU13-170**



## **1. BACKGROUND AND RATIONALE**

### **1.1. Androgen Deprivation Therapy (ADT)**

Androgen Deprivation Therapy (ADT) with Luteinizing Hormone Releasing Hormone (LHRH) agonists or antagonists in combination with androgen receptor antagonists such as bicalutamide, termed Combined Androgen Deprivation (CAD) is one of the common standard of care options in metastatic hormone naïve prostate cancer. ADT alone is also acceptable. Survival benefit of adding anti-androgen to medical or surgical castration was first shown by the SWOG-coordinated US Intergroup study SWOG-8494 (INT-0036), which randomly assigned 603 men with newly diagnosed hormone sensitive metastatic prostate cancer, to combine androgen deprivation (CAD) with leuprolide plus flutamide or leuprolide alone<sup>1</sup>. When compared to leuprolide alone, men treated with CAD had significantly longer progression-free and median survival (16.5 vs. 13.9 months, and 35.6 vs. 28.3 months, respectively). However, in a subsequent Phase III trial (SWOG-8894, INT-0105) with 1387 men, addition of flutamide to bilateral orchiectomy did not result in a clinically meaningful improvement in survival<sup>2</sup>. Although more patients treated with CAD achieved a serum PSA < 4 ng/mL (74 versus 62 percent with placebo), the differences in median and progression-free survival were not statistically significant (34 versus 30 months, and 20 versus 19 months, respectively). Since then, several meta-analyses have shown improvement in survival outcomes with CAD over castration, although with increased toxicity<sup>3-5</sup>. ASCO guidelines published in 2007 state that CAD should be considered an option, and be discussed with the patients with the emphasis that improved overall survival may occur at the cost of higher toxicity.

The PSA response to ADT at 7 months is a validated prognostic marker in metastatic prostate cancer. In the randomized phase 3 SWOG 9346 trial, the depth of PSA response (i.e. < 0.2, 0.2-4 or > 4 ng/ml at 7 months) predicted overall survival. Based on data from over 1000 patients with new M1 prostate cancer undergoing ADT with goserelin and bicalutamide in SWOG 9346, Hussain M. and colleagues have reported that failure to achieve a PSA of  $\leq 4$  ng/ml (or to be experiencing a rise in PSA) after 7 months of combined ADT is a very powerful negative predictor for survival<sup>6,7</sup>. The median overall survival for this group of patients was 20 months from the start of androgen deprivation therapy. This is to be contrasted with the 45% of the patients who achieved undetectable PSA levels ( $\leq 0.2$  ng/ml) at month 7 whose median overall survival was of 82 months from the start of androgen deprivation. Therefore, increasing the depth of the PSA response to ADT possibly by combination with novel agents is a worthy goal in newly diagnosed metastatic prostate cancer.

### **1.2. Bone metastases in newly diagnosed metastatic prostate cancer**

Bone metastases are present in nearly 90% of patients with newly diagnosed metastatic prostate cancer<sup>8</sup> and account for significant morbidity manifested as bone pain, skeletal related events (SREs) such as bone fractures, spinal cord compression, need for palliative radiation or surgery and the related cost of managing these complications. Zoledronic acid and denosumab have been shown to lower the incidence of skeletal related events in castration resistant prostate cancer but do not extend survival<sup>9,10</sup>. However, there is no proven bone targeted therapy in hormone naïve metastatic prostate cancer that improves oncologic outcomes. Effective targeting of skeletal metastasis is an important unmet need in clinical management of advanced prostate cancer.

### 1.3. Clinical Experience with Radium-223 dichloride

Radium-223 dichloride (Xofigo<sup>®</sup>) is a bone seeking alpha radiation emitting radiopharmaceutical with a short tissue penetration depth (2-10 cells deep or <100 microns). The alpha particle radiation causes double-strand breaks in DNA, killing cells. Radium-223 is given intravenously and is a calcium mimetic in that, like calcium, radium-223 accumulates preferentially in areas of bone undergoing increased turnover, such as areas where bone metastases are forming. The short tissue penetration limits damage to the surrounding tissues.

In a multicenter randomized placebo controlled phase 2 trial in patients with castration resistant prostate cancer and symptomatic bone pain needing external beam radiation therapy, radium-223 was started during external beam radiation therapy and given for 4 doses<sup>11</sup>. Median relative change in PSA from baseline to 4 weeks after last study injection was -23.8% (range -98.6 to 545.6) in the radium-223 group and +44.9% (-91.3 to 563.5) in the placebo group (p=0.003, Wilcoxon ranked-sums test). A confirmed PSA response of more than 50% was seen in 11 of 31 patients assigned radium-223 and five of 28 assigned placebo (p=0.153, Fisher's exact test). Median time to PSA progression was 26 weeks (95% CI 16-39) in the radium-223 arm compared with 8 weeks (4-12) in the placebo arm (p=0.048, log rank). Censoring for concomitant treatment that might affect PSA did not change the overall results that radium-223 was associated with improved PSA endpoints.

The randomized phase 3 trial, Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA), enrolled 921 patients with metastatic, castration-resistant prostate cancer with  $\geq 2$  symptomatic bone metastases, post-docetaxel or ineligible for docetaxel, and no visceral metastases<sup>12</sup>. Men in the trial were randomized in a 2:1 fashion to receive radium-223 (50 kBq/kg body weight given intravenously every 4 weeks for 6 doses) plus the best standard of care or a placebo plus the best standard of care. Systemic chemotherapy was not allowed during the treatment period. The primary endpoint of the trial was overall survival. Secondary endpoints included time to first symptomatic skeletal related event and quality-of-life measures.

The trial was stopped in early 2011 when a planned interim analysis by an independent data safety and monitoring committee from the trial detected that men randomized to radium-223 had statistically significantly better overall survival than men assigned to receive the placebo. Median overall survival was 14.9 months for the men assigned to receive radium-223 and 11.3 months for those assigned to the placebo (HR for death 0.695, 95% CI 0.552-0.875, p=0.002). An overall survival benefit with radium-223 was seen in all subgroups of men analyzed—for example, men benefited whatever the extent of their disease.

In the ALSYMPCA study, increase in PSA level was defined as a relative increase of  $\geq 25\%$  from the baseline level and an absolute increase of  $\geq 2$  ng per milliliter at  $\geq 12$  weeks, in patients with no decrease in the PSA level from baseline, or a relative increase of  $\geq 25\%$  and an absolute increase of  $\geq 2$  ng per milliliter above the nadir, confirmed  $\geq 3$  weeks later, in patients with an initial decrease from baseline. Radium-223 significantly prolonged the time to an increase in PSA level thus defined (HR 0.64; 95% CI, 0.54 to 0.77; P<0.001). A 30% or greater reduction in PSA blood levels at week 12 was achieved in 16% of patients in the radium-223 group and in 6% of patients in the placebo group (P<0.001).

Radium-223 also delayed time to first SRE which occurred at a median of 15.6 months versus 9.8 months in the placebo arm (HR=0.61; 95% CI 0.461-0.807, p=0.0005). Fewer men in the radium-223 group experienced serious adverse events (47 percent versus 60 percent) or stopped treatment because of adverse events (16 percent versus 21 percent) than in the placebo group. Compared with men in the placebo group, men assigned to receive radium-223 also reported a better quality of life as measured using a standard assessment tool (FACT-P). Radium-223 showed a tolerable safety profile with the most common adverse effects being bone pain and gastrointestinal toxicities (grade 3 and 4 of 1% vs. 1% in the placebo arm). Importantly, for this patient population with implications for concurrent or sequential cytotoxic chemotherapy, grade 3 and 4 hematological toxicity was uncommon (anemia in 11%, neutropenia in 2% and thrombocytopenia in 4%). On May 15, 2013, based on interim results from the ALSYMPCA trial, the FDA approved radium-223 for the treatment of men with castration-resistant prostate cancer with bone metastases that are causing symptoms.

#### **1.4 United States National Institutes of Standard and Technology (NIST)**

The quantification of radium-223 radioactivity in Xofigo (radium-223 dichloride; BAY 88-8223) is based on the primary standardization performed by the US NIST. National Institute of Standards and Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published (2).

The NIST SRM is used to calibrate the instruments in production and quality control for both the drug substance and drug product. Additionally, the NIST SRM is used to prepare the NIST traceable Ra-223 reference materials which are then sent to the end-users (e.g., nuclear medicine laboratory physicians or technicians) for dial-setting of their dose calibrators, to allow verification of the patient dose.

In 2014, NIST performed a re-assessment of the primary standardization based on preliminary information suggesting a potential discrepancy of approximately 8-10% between the published NIST primary standardization (2) and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of the re-assessment, NIST reported their findings (3) and had issued a revised NIST SRM in 2015.

The discrepancy in the NIST standardization was determined to be -9.5% between activity values obtained using the old reference standard relative to the new primary standardization. Consequently, the current numerical values were corrected by approx. + 10.5%. This update for dial settings was implemented on April 25, 2016. At the time of this update, no patients have been treated on this protocol.

#### **1.5 Role of chemotherapy with docetaxel in new hormone sensitive metastatic prostate cancer:**

ECOG 3805/CHAARTED was an intergroup Phase III study comparing ADT, with or without chemotherapy with docetaxel, with prednisone in men with hormone sensitive metastatic prostate cancer (mHSPC). The study enrolled 790 men with mHSPC between July 2006 and November 2012. Approximately two-thirds of patients had a high extent of disease which, according to the study, meant the disease involved the liver, four or more bones, or both. Results of the study were presented in the 2014 ASCO annual meeting. There was a significant improvement in the

overall survival (OS) favoring the participants who had received docetaxel chemotherapy in addition to the ADT compared to the ADT alone (57.6 vs. 44 months, HR 0.63; 95% CI: 0.48, 0.82; P = 0.0006). Further analysis showed that patients with a high extent of metastatic disease accounted for most of the benefit in the OS from docetaxel plus ADT (49.2 vs. 32.2 months, HR 0.62; 95% CI: 0.46, 0.83; P = 0.0012). Median follow-up at the time of report was 29 months, and at this time, the median survival in the low extent disease patients both arms had not been reached. These data support the use of front line docetaxel with androgen deprivation therapy for patients with newly diagnosed mHSPC who are deemed to be suitable candidates for docetaxel per the treating physician's clinical judgment.

## **1.6 Hypothesis**

We hypothesize that the combination of ADT and radium-223 dichloride will increase the depth of PSA response and will target bone metastases effectively in subjects with newly diagnosed prostate cancer and skeletal metastases, reflected in a higher percentage of subjects achieving a PSA value of 0.2 ng/mL or less ("undetectable PSA") after 7 months of combination therapy compared to ADT alone and a greater proportion of subjects normalizing an elevated serum total alkaline phosphatase level after 12 weeks of combination therapy compared to ADT alone. We will use the primary endpoint of 12-month radiologic progression free survival (rPFS). We hypothesize that if the trial meets the primary endpoint, radium-223 dichloride would be worthy of future testing in phase 3 trials.

## **2. OBJECTIVES**

### **2.1 Primary Objective**

2.1.1 Determine whether the combination of ADT plus radium-223 dichloride is more effective than ADT alone based upon radiologic progression free survival (rPFS) of subjects with newly diagnosed metastatic prostate cancer with bone metastases.

### **2.2 Secondary Objectives**

2.2.1 Assess safety and toxicity including incidence of skeletal related events (SRE) and secondary neoplasms.

2.2.2 Estimate the proportion of subjects with  $PSA \leq 0.2$  ng/mL after 7 months of androgen deprivation therapy, the proportion of subjects with  $PSA \leq 4$  ng/mL after 7 months of androgen deprivation therapy, the median time to castration resistance, 2-year PSA progression free survival proportion (PCWG2 criteria) and 2-year overall survival proportion in both arms.

2.2.3 Determine the proportion of subjects with elevated serum total alkaline phosphatase (ALP) at baseline who normalize their alkaline phosphatase after 12 weeks of therapy, assess time to ALP progression ( $\geq 25\%$  increase in ALP from baseline/nadir (whichever is lower) and above ULN), association of ALP x in both arms.

2.2.4 Evaluate change in pain level and analgesic use using the Brief Pain Inventory (BPI short form) and WHO ladder scale, respectively, with therapy.

## 2.3 Exploratory Correlative Objectives

- 2.3.1 Assess number of circulating tumor cells (CTCs) and gamma H2AX in all subjects (number of subjects = 204).
- 2.3.2 Explore the association of bone turnover markers with clinical outcome and change in serum bone turnover markers with therapy in both arms.

## 3 ELIGIBILITY CRITERIA

### 3.1 Inclusion Criteria

#### Definitions:

- **Androgen Deprivation Therapy** includes LHRH agonist or LHRH antagonist or bilateral orchiectomy. Anti-androgen receptor blockers (e.g. bicalutamide) do not constitute androgen deprivation therapy.
- **Protocol specified therapy** refers to the androgen deprivation therapy (see above) with or without radium-223 dichloride.

1. All subjects or their legally authorized representative must be informed of the investigational nature of the study and provide written informed consent and HIPAA authorization for release of personal health information before performance of any study related procedure not part of routine medical care.  
**NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Men  $\geq$  18 years of age at the time of informed consent.
3. Histological or cytological evidence of prostate adenocarcinoma.
4. All subjects must have radiologic or pathologic evidence of skeletal metastases with  $\geq$  2 skeletal lesions with or without pain at baseline on bone scan or axial imaging or with 1 skeletal lesion and bone pain within 28 days prior to the registration.
5. All subjects must have a radiographic assessment (chest or abdominal/pelvic CT or MRI) within 28 days prior to registration but do not need to have measurable disease.
6. ECOG (Eastern Cooperative Oncology Group) Performance Status of 0-2 within 28 days prior to registration (see Study Procedures Manual [SPM] for ECOG Performance Status definitions). ECOG Performance Status of 3 will only be allowed if judged by the site investigator as attributable exclusively to bone pain.
7. Subjects must fall into one of the two populations below:
  - **Early Induction Group:** Subjects who have started androgen deprivation therapy (luteinizing hormone–releasing hormone (LHRH) agonist or antagonist therapy with or without an antiandrogen agent) a maximum of 28 days before registration and who otherwise meet all the eligibility criteria.
  - **Late Induction Group:** Subjects who have NOT started any androgen deprivation therapy (luteinizing hormone–releasing hormone (LHRH) agonist or antagonist therapy with or without an antiandrogen agent).

8. Anti-androgen receptor antagonist therapy must be bicalutamide. Subjects already started on other anti-androgens must be willing to switch over to bicalutamide.
9. Any prior androgen-deprivation therapy or finasteride as neoadjuvant or adjuvant therapy or for biochemical recurrence must have been discontinued at least 6 months prior to registration.
10. Prior surgical treatment for prostate cancer is allowed but must have been completed at least 14 days prior to registration and any toxicity from such therapy must have recovered to  $\leq$  grade 1 per CTCAE version 4 criteria by the time of registration.
11. The following laboratory values must be obtained within 28 days prior to registration for protocol therapy.
  - Hemoglobin (Hgb)  $\geq$  8.0 g/dL (80 g/L) without packed RBC transfusion
  - Platelets  $\geq$  100 K/mm<sup>3</sup>
  - Absolute neutrophil count (ANC)  $\geq$  1.5 K/mm<sup>3</sup>
  - Total Bilirubin  $\leq$  2  $\times$  institutional upper limit of normal (ULN) except subjects with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL
  - Aspartate aminotransferase (AST, SGOT)  $\leq$  2.5 $\times$  institutional ULN ( $\leq$  5  $\times$  institutional ULN in the presence of liver metastases).
  - Alanine aminotransferase (ALT, SGPT)  $\leq$  2.5 $\times$  institutional ULN ( $\leq$  5  $\times$  institutional ULN in the presence of liver metastases).
  - Estimated Creatinine Clearance by Cockcroft-Gault formula  $\geq$  30 mL/min
12. All subjects, including those who are surgically sterilized, must be willing to use an effective method of contraception (barrier method of birth control or abstinence) from the time informed consent is signed until 6 months after completion of protocol therapy.
13. Subjects must consent to bank whole blood, serum, plasma for future unspecified studies.
14. Patients with 'high extent or extensive stage' of metastases (per CHAARTED (E3805) study: visceral metastasis or more than 4 bone metastases including at least 1 non-axial bone metastasis or both) should be considered unsuitable candidates for docetaxel per the treating physician's clinical judgment, or should have declined docetaxel therapy.

### 3.2 Exclusion Criteria

1. Prior cytotoxic chemotherapy for metastatic prostate cancer. Prior cytotoxic chemotherapy with curative intent in the neoadjuvant or adjuvant setting is allowed but must have been completed at least 6 months prior to registration. No cytotoxic chemotherapy is allowed during protocol specified therapy.
2. Prior concomitant therapy with ketoconazole, aminoglutethimide or abiraterone acetate or enzalutamide (MDV3100) or intent to treat with the above. Concurrent megestrol for hot flashes is allowed.
3. Prior or ongoing bisphosphonate (e.g. zoledronic acid) or RANKL inhibitor (e.g. denosumab) use is NOT allowed except when used solely for osteoporosis and strictly per guidelines for that indication. Bisphosphonate or RANKL inhibitor cannot be initiated for any indication during protocol specified therapy without consent of the sponsor-investigator of the study.
4. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186 or rhenium-188.

5. Diagnosis of aplastic anemia, pure red cell aplasia, myelodysplasia or any of the other bone marrow failure states.
6. Any neuroendocrine differentiation including small cell carcinoma on histology or cytology.
7. No prior malignancy **except** for non-melanomatous skin cancer or non-muscle invasive bladder cancer or adequately treated Stage I or II cancer (adequacy at discretion of treating investigator) from which the subject is currently in complete remission, or any other cancer from which the subject has been disease-free for at least 3 years.
8. History of or active CNS metastasis (brain, leptomeningeal or cord compression). Brain imaging studies are not required for eligibility if the subject has no neurologic signs or symptoms suggestive of brain metastasis. Subjects with neurological symptoms are recommended to undergo a head CT scan (with or without intravenous contrast) or brain MRI (with or without intravenous contrast) to exclude brain metastasis. If brain imaging studies are performed, they must be negative for CNS disease. Skull bone involvement without neurological impact by prostate cancer is allowed.
9. Treatment with any other investigational agent within 28 days prior to registration. Subjects must not be treated with any other investigational agent while on protocol specified therapy.
10. Prior hemibody external radiation. Any external radiation therapy must have been completed at least 14 days prior to registration. Any toxicity from such therapy must have recovered to  $\leq$  grade 1 per CTCAE version 4 criteria by the time of registration.
11. Clinically significant infections as judged by the site investigator. Subjects must not have been diagnosed with human immunodeficiency virus (HIV) infection, active chronic hepatitis B or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with participation in this study. Subjects should be tested for hepatitis B or C or HIV infection during screening only if they are considered by the investigator to be at high risk for these infections.
12. Known hypersensitivity to bicalutamide.
13. Known gastrointestinal (GI) disease or procedure that could interfere with the GI absorption or tolerance of bicalutamide, including difficulty swallowing oral medications.
14. Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., subjects with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), symptomatic pulmonary embolism within 3 months, unstable angina pectoris, myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia as determined by the treating physician.

#### **4 SUBJECT REGISTRATION**

All subjects must be registered and randomized through the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system OnCore. A subject is considered registered when an "On Study" date is entered into OnCore. Subjects must be registered prior to randomization. Subjects must begin therapy **within 5 business days** of randomization.

#### 4.1 STRATIFICATION FACTORS

Subjects will be stratified based on serum total alkaline phosphatase at baseline and extent of disease (described below). Randomization will occur within stratification group.

- Extent of Disease: <6 skeletal metastases with no visceral metastases versus  $\geq 6$  skeletal metastases or visceral metastases.
- Serum total alkaline phosphatase at baseline: Normal vs Abnormal. Abnormal alkaline phosphatase is defined as > 130 IU/L.
- Early Induction or Late Induction status will not be a stratification criterion.

### 5 TREATMENT PLAN

#### 5.1 Treatment schedule

Subjects will be randomized in a 2:1 ratio in favor of the experimental arm to one of the following treatments:

- Arm A (Control): LHRH agonist/antagonist + bicalutamide
- Arm B (Experimental): LHRH agonist/antagonist + bicalutamide + radium-223 dichloride

#### 5.2 Androgen Deprivation Therapy

- All subjects will receive androgen deprivation therapy with a LHRH agonist (any LHRH agonist such as leuprolide acetate or goserelin acetate is acceptable) or a LHRH antagonist (degarelix) or bilateral orchiectomy per the treating physician. Androgen Deprivation therapy with LHRH agonist or LHRH antagonist will be given continuously.
- LHRH Agonist will be given as approved for androgen deprivation at a dose necessary to maintain castrate levels and equivalent to 22.5 mg of Leuprolide IM every 3 months. One, three, four and six month or one year depot injections are acceptable.
- If LHRH Antagonist (Degarelix) is chosen as the method of androgen deprivation therapy, it will be given as approved: Initial, 240 mg subcutaneously given as 2 injections of 120 mg each and subsequent maintenance doses of 80 mg subcutaneously every 28 days.
- A delay of up to 7 days in administering a scheduled dose of LHRH agonist or LHRH antagonist is allowed.

#### 5.3 Androgen Receptor Antagonist

All subjects will receive bicalutamide. Subjects may start bicalutamide within 14 days prior to starting a LHRH agonist/antagonist or the date of bilateral orchiectomy at the discretion of the treating investigator to prevent a clinical flare reaction. Subjects on other anti-androgens prior to registration must switch to bicalutamide without lead-in.

#### 5.4 Radium-223 dichloride

- Radium-223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0-8.0. The radioactive concentration at the reference date is 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.

- The volume per vial is 6 mL, corresponding to 6.6 at the reference day. Radium-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
- Current NIST standard: Radium-223 dichloride, 55 kBq/kg body weight, will be administered as a bolus intravenous (IV) injection (up to 1 minute) at intervals of every 28 days for up to 6 cycles. Subjects randomized to this arm will begin treatment on C2D1.
- The dose of radium-223 dichloride will be recalculated prior to each dose and will be based on the most recent actual body weight, recorded within 4 weeks.
- There must be a minimum of 25 days between consecutive radium-223 dichloride doses.
- The following hematologic criteria must be met within 3 days prior to first dose of Radium 223:
  - ANC  $\geq$  1.5 K/ mm<sup>3</sup>
  - Platelets  $\geq$  100 K/mm<sup>3</sup>
  - Hemoglobin  $\geq$  8 g/dL (80 g/L) without PRBC transfusion
- The following hematologic criteria must be met within 3 days prior to administration of remaining doses:
  - ANC  $\geq$  1.0 K/ mm<sup>3</sup>
  - Platelets  $\geq$  50 K/mm<sup>3</sup>
  - Hemoglobin  $\geq$  8 g/dL (80 g/L) with or without PRBC transfusion
- Infusions of radium-223 dichloride may be given within a window of -3 days to +7 days for reasons including observed holidays, inclement weather, scheduling conflicts, etc. Schedule changes should be clearly documented in the source documents and electronic case report forms. Please see Decay Factor Table if date of radium-223 dichloride changes from originally planned.

## 5.5 Designation of Cycle 1 Day 1 date

Cycle 1 Day 1 is designated as the day the subject receives LHRH agonist or antagonist (androgen deprivation therapy) or the date of bilateral orchiectomy. The early induction subjects will have already received their first LHRH agonist or antagonist injection or had bilateral orchiectomy. Please verify this date for early induction subjects with source documentation.

### 5.5.1 Treatment schedule Arm A (Control)

AGENT	DOSE	ROUTE	DAYS
<b>LHRH agonist/antagonist</b>	As per treating physician See 5.2	According to package insert	According to package insert
<b>Bicalutamide</b>	50 mg	Oral (PO)	Daily

### 5.5.2 Treatment schedule Arm B (Experimental)

AGENT	DOSE	ROUTE	DAYS
<b>LHRH agonist/antagonist</b>	As per treating physician See 5.2	According to package insert	According to package insert
<b>Bicalutamide</b>	50 mg	Oral (PO)	Daily
<b>Standard for Radium-223 dichloride</b>	55 kBq (1.5 microcurie) per kg body weight	Intravenous (IV bolus)	Every 28 days for 6 injections

### 5.5.3 Continuation of ADT/completion of Radium-223

After the completion of seven cycles of ADT, further treatment with androgen deprivation will be up to the treating physician. If radium-223 dichloride doses have been delayed for any reason and all 6 doses have not been administered by the 28 weeks' time-point, they may be administered later at the discretion of the site investigator provided laboratory parameters as outlined above are satisfied. The site investigator/site should record data on such delayed radium-223 administrations including dose of radium-223 dichloride, date of administration and hematological parameters obtained within 3 days of administration.

### 5.6 PSA Assessments

PSA values will be assessed:

- PSA obtained prior to initiating androgen deprivation therapy, should be used as the baseline PSA. For subjects in the early induction group, if a baseline PSA prior to initiation of ADT is not available, the baseline PSA will be considered the value obtained prior to randomization.
- Prior to randomization then
- Day 1 of every Cycle through Cycle 12 then
- Every 3 months for the following year
- More frequent PSA monitoring as clinically indicated is acceptable.

### 5.7 Pre-medication

Institutional standards should be followed for hydration and pre-medications for LHRH agonists or antagonists. No pre-medications are needed prior to the first dose of radium-223 dichloride. Anti-emetics may be used subsequently as clinically indicated.

### 5.8 Concomitant Medications

The use of supportive care medications is allowed according to institutional standards. We strongly recommend supplemental calcium 1200 mg daily and Vitamin D3 1000 IU daily.

However, certain medications are specifically disallowed.

- Five-alpha reductase inhibitors (e.g. finasteride and dutasteride) are not permitted.
- Other excluded therapies include ketoconazole, aminoglutethimide, abiraterone acetate, enzalutamide (MDV3100), diethylstilbestrol (DES), and other estrogen preparations.
- Cytotoxic chemotherapy is not allowed during protocol specified therapy.

## 5.9 Supportive Care

- Institutional standards should be followed for hydration and pre-medications.
- The use of packed red blood cell transfusions is allowed as clinically indicated per institutional guidelines or at investigator's discretion but must be clearly documented in the source documents.
- Palliative external beam radiation therapy for prostate cancer during protocol specified therapy is allowed as clinically indicated. Radium-223 dichloride doses must be held during external beam radiation therapy and may resume after a minimum of 7 days after completion of external beam radiation if hematological laboratory parameters are adequate (see section 5).
- Palliative external beam radiation therapy can start without a minimum time interval after a radium-223 dose as clinically indicated.
- Colony stimulating factors (e.g. G-CSF or GM-CSF) are not allowed during protocol specified therapy.
- Prolonged use of systemic corticosteroids for prevention of allergic reactions is discouraged because of their potential to cause and exacerbate hyperglycemia. Intermittent use of corticosteroids is permitted.

## 6 TREATMENT MODIFICATIONS

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the treatment phase of the study.

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) v4 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE v4 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE v4.

### 6.1 Treatment-Limiting Adverse Events

A treatment-limiting adverse event is any adverse event related to protocol therapy experienced during the study resulting in treatment termination.

### 6.2 General Treatment Modification Considerations

- If multiple toxicities are experienced, treatment modifications will be based on the toxicity requiring the largest dose reduction.

#### 6.2.1 Modifications for Androgen Deprivation Therapy (ADT) and Bicalutamide

- Delay of up to 7 days in administering the scheduled dose of LHRH agonist or antagonist is allowed
- Missed doses of bicalutamide are to be omitted rather than made up.

##### 6.2.1.1 Modifications for Hematologic Toxicity:

Use of granulocyte colony stimulating factors is not permitted.

### 6.2.1.2 Modifications for Non-Hematologic Toxicity:

#### Diarrhea:

The major toxic effect of bicalutamide is moderate diarrhea which is rarely severe (exclusion of other causes of diarrhea should be considered in severe cases). The modifications for toxicity related to diarrhea will be as follows:

- Grade  $\geq 3$  diarrhea, permanently discontinue bicalutamide
- Grade 2 diarrhea, treat symptomatically with anti-diarrhea drugs.
- Grade 2 diarrhea unresponsive to symptomatic treatment- hold bicalutamide until diarrhea resolves to  $\leq$  Grade 1.

In case of any diarrhea  $\geq$  Grade 1, the following tests are recommended at the discretion of the site investigator as clinically indicated:

- WBC in stools
- Stool cultures
- Clostridium difficile titers
- Further testing will be at the discretion of the site investigator

#### Abnormal Liver Function Tests (SGOT/AST, SGPT/ALT, Bilirubin):

- Grade  $\geq 3$ , permanently discontinue bicalutamide
- Grade 2 toxicity
  - Hold bicalutamide and recheck liver function tests weekly until LFTs are normal (Grade 0). LFTs may be performed more frequently at the discretion of the treating physician.
  - Hepatitis screening (A, B, C) is recommended in cases of abnormal LFTs which could be consistent with infectious hepatitis.
  - Restart bicalutamide when LFTs return to normal. If the toxicity (Grade  $\geq 2$ ) recurs or if the subject requires a delay greater than 28 days, discontinue bicalutamide. Subjects will remain on protocol therapy with ADT and, if applicable, radium-223 dichloride.
- Symptoms such as flatulence, bloating and mild "gas pains" should not result in changes in bicalutamide, ADT or radium treatment. Symptomatic treatment should be employed with antacids, simethicone, etc.
- Asymptomatic Grade 3 or 4 laboratory findings, which are not considered clinically significant, may not require dose modification (i.e., dose hold). The decision to hold the dose should be based on the site investigator's clinical judgment.
- For any other Grade 3-4 adverse events, hold bicalutamide; wait until adverse event has resolved to Grade  $\leq 1$ , and then restart bicalutamide.

### 6.2.2 Modifications for Radium-223 dichloride

- Delay of up to 8 weeks (56 days) is allowed for radium-223 dichloride doses if necessitated by inadequacy of hematologic parameters or drug non-availability or necessary time interval between 2 consecutive radium-223 dichloride doses.
- A delay of 7 days is allowed for scheduling factors. There must be a minimum of 25 days between consecutive radium-223 dichloride doses.

- Every effort should be made to administer the full dosing regimen of Radium-223 dichloride. Adjustment of dose is not permitted.
- Study visits during the treatment period should occur at 28-day intervals. Dosing delays may be instituted under the following circumstances listed below.

#### **6.2.2.1 Modifications for Hematologic Toxicity:**

The following hematologic criteria must be met within 3 days prior to first dose of Radium 223:

- ANC  $\geq 1.5$  K/ mm<sup>3</sup>
- Platelets  $\geq 100$  K/mm<sup>3</sup>
- Hemoglobin  $\geq 8$  g/dL (80 g/L) without PRBC transfusion

The following hematologic criteria must be met within 3 days prior to administration of remaining doses:

- ANC  $\geq 1.0$  K/ mm<sup>3</sup>
- Platelets  $\geq 50$  K/mm<sup>3</sup>
- Hemoglobin  $\geq 8$  g/dL (80 g/L) with or without PRBC transfusion

If the hematologic parameters listed above are not met:

- Radium-223 dichloride will be held.
- Complete blood counts (CBC) will be measured weekly. Once the counts recover, radium-223 dichloride may resume at the same dose level.
- ADT and bicalutamide will continue without interruption.
- If there is no recovery to these values within 8 weeks after the last administration of radium-223 dichloride, despite receiving supportive care including blood transfusions as clinically indicated, further treatment with radium-223 dichloride will be discontinued. ADT and bicalutamide can continue and the subject will remain on study.

#### **6.2.2.2 Modifications for Non-Hematologic Toxicity:**

For Grade 4 toxicity possibly attributed to radium-223 dichloride

- Discontinue radium-223 dichloride

For Grade  $\geq 2$  toxicity attributable to radium-223 dichloride

- Radium-223 dichloride will be held until the toxicity has resolved to  $\leq$  Grade 1 or baseline.
- Supportive care should be instituted as clinically indicated.
- Once the toxicity resolves, radium-223 dichloride may resume at the same dose level.
- ADT and bicalutamide will continue without interruption.

If there is no recovery to these values within 8 weeks (56 days) after the last administration of radium-223 dichloride, despite receiving supportive care including blood transfusions as clinically indicated, further treatment with radium-223 dichloride will be discontinued. ADT and bicalutamide can continue and the subject will remain on study.

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## 7 STUDY CALENDAR & EVALUATIONS

Early Induction Subjects = Have started ADT prior to being screened for study.

Late Induction Subjects = Have NOT started ADT prior to being screened for this study

Study Day  Induction and Post Induction Cycles = 28 days (4 weeks)  Maintenance Cycles = 84 days (12 weeks)	Screening (0 - 28 days) <sup>1</sup>	Induction Cycle 1 <sup>12</sup>	Induction Cycles 2-7	Post Induction Cycle 8	Post Induction Cycles 9-12	Maintenance Cycle 13	Maintenance Cycles 14-16 <sup>13</sup>	Maintenance Cycle 17	End of Treatment and Follow up <sup>14</sup>	
		Day 1	Day 1 (±3)	Day 1 (±7)	Day 1 (±7)	Day 1 (±7)	Day 1 (±14)	Day 28 (±7)	Day 1	
<b>REQUIRED ASSESSMENTS</b>										
Informed Consent	X									
Medical History and Diagnosis/Staging	X									
Physical examination <sup>2</sup>	X	X	X	X		X		X		
Vital signs including BP, weight, height (screening ONLY) and ECOG PS	X	X	X	X		X		X		
CBC with diff and platelet <sup>3</sup>	X	X <sup>12</sup>	X	X		X		X		
CMP, Mag, and Phos. <sup>3</sup>	X	X <sup>12</sup>	X	X		X		X		
Alk Phos, PSA <sup>4</sup>	X	X <sup>12</sup>	X	X	X	X	X	X	X	
Testosterone <sup>5</sup>	X	X <sup>12</sup>		X		X				
AEs & concomitant medications <sup>6</sup>	X	X	X	X	X	X	X	X	X	
BPI (short form), WHO ladder <sup>7</sup>		X <sup>6</sup>	X <sup>7</sup>	X						
<b>DISEASE ASSESSMENT</b>										
CT or MRI abdomen/pelvis <sup>8</sup>	X			X		X		X		
Chest X-ray or CT chest if clinically indicated <sup>8</sup>	X			X		X		X		
CT or MRI Brain if clinically indicated <sup>8</sup>	X			X		X		X		
Bone Scan <sup>8</sup>	X			X		X				
DEXA scan <sup>8</sup>	X					X				
<b>TREATMENT EXPOSURE<sup>9</sup></b>										
<b>Arm A (Control)</b>										
LHRH agonist/antagonist + Bicalutamide		X	—————→							
<b>Arm B (Experimental)</b>										
LHRH agonist/antagonist + Bicalutamide		X	—————→							
Radium-223 dichloride			X							

Study Day	Screening (0 - 28 days) <sup>1</sup>	Induction Cycle 1 <sup>12</sup>	Induction Cycles 2-7	Post Induction Cycle 8	Post Induction Cycles 9-12	Maintenance Cycle 13	Maintenance Cycles 14-16 <sup>13</sup>	Maintenance Cycle 17	End of Treatment and Follow up <sup>14</sup>
Induction and Post Induction Cycles = 28 days (4 weeks)									
Maintenance Cycles = 84 days (12 weeks)		Day 1	Day 1 (±3)	Day 1 (±7)	Day 1 (±7)	Day 1 (±7)	Day 1 (±14)	Day 28 (±7)	Day 1
<b>CORRELATIVE STUDIES</b>									
Serum for Bone Turnover Markers <sup>10</sup>		X <sup>10</sup>	X <sup>10</sup>						X <sup>10</sup>
Circulating Tumor Cells (CTCs) <sup>10</sup>		X <sup>10</sup>	X <sup>10</sup>						X <sup>10</sup>
<b>BANKING SAMPLES</b>									
Whole Blood <sup>11</sup>		X <sup>11</sup>	X <sup>11</sup>						X <sup>11</sup>
Serum and plasma <sup>11</sup>		X <sup>11</sup>	X <sup>11</sup>						X <sup>11</sup>
<b>FOLLOW UP</b>									
Survival									X
Secondary Malignancies									X

**Footnotes: Please NOTE: unless otherwise specified, all testing will be performed in BOTH arms.**

- NOTE:** Early induction subjects will have initiated ADT prior to registration. Results of screening procedures should be obtained through medical records if available including start date ADT therapy.
- Close monitoring for fractures should be done during the physical exam. If a fracture is suspected, radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- CBC w/diff and platelet to include: WBC with differential and platelets, hemoglobin and hematocrit. Additional monitoring of CBC w/diff and platelet per site investigator's discretion based on subject clinical status. CMP blood chemistries to include: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin. Magnesium and phosphorus to be included.
- PSA, Alk Phos to be assessed Cycle 1 Day 1 (late induction group) or Cycle 2 Day 1 (early induction group). Subjects will be followed for PSA and Alk Phos every month for a total of 1 year from randomization then every 12 weeks (± 14 days) for the next year (2 years from randomization). If a subject withdraws consent, he is deemed "off study" and will NOT be followed further.
- Testosterone (serum) will be measured on Cycle 1 Day 1 (for late induction group only), Cycle 8 Day 1 (both early and late induction groups) and after 12 months of ADT. For early induction subjects, a testosterone value prior to initiation of ADT should be obtained via medical records, if available. If the result is not available, subjects are not ineligible for study.
- AE and concomitant medication assessment: AE assessment should include a review of any symptoms the subject may be experiencing. In addition, the subject should be assessed for secondary malignancies. Concomitant medication review will include all medications the subject is taking.
- Pain assessment with BPI (short form) and assessment of analgesic use with WHO ladder scale will be performed at 3 time-points: Cycle 1 Day 1 (late induction group) or Cycle 2 Day 1 (early induction group), on Cycle 4 Day 1 and Cycle 8 Day 1.
- CT and MRI scans if clinically indicated can be performed with or without intravenous contrast as per institutional guidelines at screening, C8D1, C13D1 and C17D28 (a window of ± 7 days for all scans is allowed). DEXA scan will be performed at screening and after completion of 1 year of treatment. CT or Brain MRI: Brain imaging studies are not required for eligibility if the subject has no neurologic signs or symptoms suggestive of brain metastasis. Subjects

with neurological symptoms are recommended to undergo a head CT scan (with or without intravenous contrast) or brain MRI (with or without intravenous contrast) to exclude brain metastasis. If brain imaging studies are performed, they must be negative for CNS disease. Skull bone involvement without neurological impact by prostate cancer is allowed. A bone scan will be performed at baseline, C8D1 and after completion of 1 year of treatment.

9. All subjects will receive androgen deprivation therapy with a LHRH agonist (any LHRH agonist such as leuprolide acetate or goserelin acetate is acceptable) or a LHRH antagonist (degarelix) or bilateral orchiectomy per the treating physician. Androgen Deprivation therapy with LHRH agonist or LHRH antagonist will be given continuously.
10. MANDATORY: Serum submission for Bone Turnover Markers: Pre-Dose Cycle 1 Day 1 (late induction group) and thereafter on Day 1 of each cycle during the remaining 6 months of protocol specified therapy and at End of Treatment (both induction groups). CTCs: For following time points only: C1D1 (late induction group only); C2D1 (early induction group only); C4D1; EOT visit. CTCs will be collected for all subjects (n = 204). See Correlative Laboratory Manual (CLM) for collection, labeling and shipping instructions.
11. MANDATORY: Whole blood for banking is to be collected pre dose Cycle 1 Day 1 (late induction group) or pre dose Cycle 2 Day 1 (early induction group) and at EOT. Serum and plasma are to be collected at Pre-Treatment Cycle 1 Day 1 (late induction group) or Cycle 2 Day 1 (early induction group) and at EOT. See CLM for collection, labeling, processing and shipping instructions.
12. For late induction subjects, Cycle 1 Day 1 will occur after screening and upon completion of eligibility. C1D1 lab testing need not be repeated if completed within 7 days of starting protocol therapy. For early induction subjects, C1D1 occurs prior to screening; documentation of initiation of ADT (C1D1) should occur after review of the subject chart and completion of eligibility.
13. For maintenance Cycles 14-17, subjects will continue to be followed every 12 weeks for alkaline phosphatase, PSA values and AE/concomitant medication updates, initiation of new anti-cancer therapy and occurrence of secondary malignancies. This information may be obtained via local treating physician medical records.
14. The end of treatment/follow up column will be utilized for subjects that come off protocol therapy (both Arm A and Arm B) for toxicity or progression. If this occurs, subjects should have an end of treatment visit 30 days ( $\pm$  7 days) after discontinuation of protocol therapy. Subjects will then continue to be followed every 3 months for a total of 2 years from the date of randomization. If a subject withdraws consent, he is deemed "off study" and will NOT be followed further. Follow up may occur via phone call, email or other communication. If available by medical record review, alk phos, PSA, AE/concomitant medication should be obtained.

### 7.1 Screening within 28 days prior to registration for protocol therapy

- Informed Consent
- Medical history including diagnosis and staging information. For **early** induction subjects, note details of ADT therapy initiation during medical history. This review should also include laboratory values and radiology imaging completed prior to and during ADT.
- Physical examination and history of secondary malignancies. Close monitoring for fractures should be done during all physical exams. If a fracture is suspected radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- Vital signs including BP measurement, height (screening only) and weight, and ECOG performance status.
- Assessment of adverse events and concomitant medications
- Laboratory Testing:
  - Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin), magnesium, phosphorus,
  - CBC (WBC with differential and platelet count, hemoglobin and hematocrit)
  - Testosterone; Late induction subjects; may be done during screening or prior to C1D1 treatment for. Early induction subjects; if available, an alkaline phosphatase prior to initiation of ADT should be obtained through medical record review or prior to treatment C2D1.
  - Alkaline phosphatase; Late induction subjects; may be done during screening or prior to C1D1 treatment for. Early induction subjects; if available, an alkaline phosphatase prior to initiation of ADT should be obtained through medical record review or prior to treatment C2D1.
  - PSA; Late induction subjects; may be done during screening or prior to C1D1 treatment for. Early induction subjects; if available, an alkaline phosphatase prior to initiation of ADT should be obtained through medical record review or prior to treatment C2D1.
- Imaging:
  - CT or MRI abdomen/pelvis,
  - DEXA scan
  - Bone Scan
  - CT or MRI Brain, Chest X-Ray or Chest CT if clinically indicated. See eligibility criteria.

**NOTE: Subjects that have NOT received any ADT prior to screening are considered “Late Induction” and subjects that have initiated ADT prior to screening are considered “Early Induction.”**

## 7.2 Induction: Cycle 1 Day 1

**NOTE:** Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy. C1D1 is retrospective for early induction group and verified during Medical History with review of medical records.

- Physical examination. Close monitoring for fractures should be done during all physical exams. If a fracture is suspected radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- Vital signs including BP measurement, weight, ECOG performance status
- Assessment of adverse events and concomitant medications
- Laboratory Testing:
  - CMP to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin. Including magnesium, phosphorus
  - CBC (WBC with differential and platelet count, hemoglobin and hematocrit) Additional monitoring of CBC w/diff and platelet per site investigator's discretion based on subject clinical status.
  - Serum testosterone; late induction subjects. If done at screening, no need to repeat
  - Alkaline phosphatase; late induction subjects. If done at screening, no need to repeat
  - PSA; late induction subjects. If done at screening, no need to repeat
- Correlative Studies for late induction group:
  - Serum bone turnover markers collected pre-dose
  - Circulating tumor cell's (CTCs) collected pre-dose
  - Banking Samples (pre-dose): whole blood, serum, plasma
- Surveys: pain assessment with BPI (short form) and WHO ladder

## 7.3 Induction: Cycle 2 - Cycle 7 Day 1 ( $\pm 7$ days)

- Physical examination. Close monitoring for fractures should be done during all physical exams. If a fracture is suspected radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- Vital signs including BP measurement, weight, ECOG performance status
- Assessment of adverse events and concomitant medications.
- Laboratory Testing:
  - CMP to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin. Including magnesium, phosphorus
  - CBC (WBC with differential and platelet count, hemoglobin and hematocrit) Additional monitoring of CBC w/diff and platelet per site investigator's discretion based on subject clinical status
  - Serum testosterone
  - Alkaline phosphatase
  - PSA
- Correlative Studies:
  - Serum bone turnover markers collected pre-dose

**EARLY INDUCTION ONLY Cycle 2 Day 1 (In addition to the testing listed above)**

- Alkaline phosphatase
- PSA
- Correlative Studies:
  - Circulating tumor cell's (CTCs): collected pre-dose
  - Banking Samples: whole blood, serum, plasma collected pre-dose
- Surveys: pain assessment with BPI (short form) and WHO ladder.

**7.4 Cycle 4 Day 1 (in addition to testing listed above)**

- Correlative Studies:
  - Circulating tumor cell's (CTCs): collected
- Surveys: pain assessment with BPI (short form) and WHO ladder.

**7.5 Post Induction Cycle 8 Day 1 ( $\pm$  7 days)**

- Physical examination. Close monitoring for fractures should be done during all physical exams. If a fracture is suspected radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- Vital signs including BP measurement, weight, ECOG performance status
- Assessment of adverse events and concomitant medications.
- Laboratory Testing:
  - CMP to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin. Including magnesium, phosphorus
  - CBC (WBC with differential and platelet count, hemoglobin and hematocrit) Additional monitoring of CBC w/diff and platelet per site investigator's discretion based on subject clinical status
  - Testosterone
  - Alkaline phosphatase
  - PSA
- Surveys: pain assessment with BPI (short form) and WHO ladder.
- Imaging:
  - CT or MRI abdomen/pelvis
  - Bone Scan
  - Chest x-ray or Chest CT if clinically indicated

**7.6 Post Induction Cycles 9-12 ( $\pm$  7 days)**

**NOTE:** ADT may continue for up to 2 years from randomization

- Laboratory tests D1 of each cycle:
  - PSA
  - Alkaline phosphatase
- Assessment of adverse events and concomitant medications. This may be done via email, phone call or medical record review

### 7.7 Maintenance: Cycle 13 Day 1; 12 months from ADT initiation ( $\pm 7$ days):

- Clinical: Physical examination including BP measurement, weight, ECOG performance status, assessment of adverse events and concomitant medications. Close monitoring for fractures should be done during all physical exams. If a fracture is suspected radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- Laboratory Testing:
  - CMP to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, magnesium, phosphorus
  - CBC (WBC with differential and platelet count, hemoglobin and hematocrit)
  - Serum testosterone
  - Alkaline phosphatase
  - PSA
- Imaging:
  - CT or MRI abdomen/pelvis
  - DEXA scan
  - Bone Scan
  - Chest x-ray or Chest CT if clinically indicated

### 7.8 Maintenance Cycles 14-16 Day 1 ( $\pm 14$ days)

**NOTE:** ADT may continue for up to 2 years from randomization. Maintenance Cycles will = 84 days/12 weeks.

- Laboratory tests:
  - PSA
  - Alkaline phosphatase
- Assessment of adverse events and concomitant medications. This may be done via email, phone call or medical record review

### 7.9 Maintenance Cycle 17 Day 28

- Physical examination. Close monitoring for fractures should be done during all physical exams. If a fracture is suspected radiological exams should be performed per clinical guidelines. Subjects should be encouraged to contact the site investigator for any new onset pain or increase in pain in sites of known bone disease.
- Vital signs including BP measurement, weight, ECOG performance status
- Assessment of adverse events and concomitant medications.
- Laboratory Testing:
  - CMP to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), serum creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin. Including magnesium, phosphorus
  - CBC (WBC with differential and platelet count, hemoglobin and hematocrit)  
Additional monitoring of CBC w/diff and platelet per site investigator's discretion based on subject clinical status
  - Alkaline phosphatase
  - PSA

- Imaging:
  - CT or MRI abdomen/pelvis
  - Chest x-ray or Chest CT if clinically indicated

### 7.10 End of Treatment (EOT) and Follow Up

The end of treatment/follow up column will be utilized for subjects that come off protocol therapy (radium-223 dichloride if randomized to that Arm and ADT) for toxicity or progression. If this occurs, subjects should have an end of treatment visit 30 days ( $\pm$  7 days) after discontinuation of protocol therapy. Subjects will then continue to be followed every 3 months for a total of 2 years from the date of randomization. Follow up may occur via phone call, email or other communication. If available by medical record review, alk phos, PSA, AE/concomitant medication should be obtained. Testing to be done at the EOT visit:

- Circulating tumor cell's (CTCs)
- Serum bone turnover markers
- Banking Samples: serum, plasma
- Alkaline phosphatase
- PSA

If a subject withdraws consent, he is deemed **“off study”**. “Off study” subjects will not be followed further.

A subject will be discontinued from the protocol specified therapy under the following circumstances:

- If there is evidence of radiologic disease progression or symptomatic deterioration despite castration range serum testosterone level ( $< 50$  ng/dL). Such subjects can go on to other treatment outside the study as clinically indicated including continuation or initiation of radium-223 dichloride therapy. They will remain on follow-up portion of the study for a total of 2 years from the date of randomization.
- If there is development of castration-resistant prostate cancer by PSA criteria in conjunction with castration range serum testosterone level ( $< 50$  ng/dL). Castration resistant prostate cancer is defined as two consecutive increases in PSA over the nadir PSA, at least two weeks apart **AND** an absolute increase of at least 2 ng/mL from the nadir PSA (or from baseline PSA if there was no drop in PSA after starting treatment). Discontinuation of bicalutamide may be attempted at the investigator's discretion in such cases and would NOT constitute going “off treatment”. If no response to bicalutamide discontinuation, such subjects may receive other treatment outside the study as clinically indicated including continuation or initiation of radium-223 dichloride therapy. They will remain on follow-up portion of the study for a total of 2 years from the date of randomization.
- If a subject requests to discontinue protocol specified therapy for any reason at any time. Subjects can stop protocol therapy at any time (off treatment). Such subjects may receive other treatment outside the study as clinically indicated including continuation or initiation of radium-223 dichloride therapy. However, subjects will continue to be followed for survival status and for secondary malignancies as reported by subjects every 3 months for a total of 2 years from the date of randomization unless they withdraw consent (if consent withdrawn, they will be deemed to be off study).

- If androgen deprivation therapy exhibits unacceptable toxicity. Such subjects may receive other treatment outside the study as clinically indicated including continuation or initiation of radium-223 dichloride therapy. **NOTE:** Subjects off bicalutamide or radium-223 dichloride for toxicity but continuing on LHRH agonist/antagonist or have had surgical castration remain on protocol specified therapy.
- If **ALL** protocol specified therapy is interrupted for > 28 days due to a treatment related adverse event. **NOTE:** A delay of up to 7 days in administering the scheduled dose of LHRH agonist or LHRH antagonist is allowed. A delay of up to 56 days in administering the scheduled dose of radium-223 dichloride is allowed if it is due to inadequate hematologic parameters or drug supply issues.

All reasons for protocol therapy discontinuation must be clearly documented.

**8. CRITERIA FOR DISEASE EVALUATION AND ENDPOINT DEFINITIONS**  
RECIST 1.1 criteria will apply to only soft tissue lesions. PCWG2 criteria will apply to bone lesions and PSA values.

### **8.1 Measurability of lesions**

#### **8.1.1 Measurable disease**

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 2.0$  cm by chest x-ray, by  $\geq 1.0$  cm with CT or MRI scans, or  $\geq 1.0$  cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if they measure  $\geq 1.5$  cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

#### **8.1.2 Non-measurable disease**

All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with  $\geq 1.0$  cm to <1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable, as are previously radiated lesions that have not progressed.

### 8.1.3 Notes on measurability

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

2. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
3. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.
4. If a target lesion becomes very small, some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0 cm should be recorded.

## 8.2 Progression Criteria

**8.2.1 PSA progression** is defined by two consecutive increases in PSA over the nadir PSA, at least two weeks apart AND an absolute increase of at least 2 ng/mL from the nadir PSA (or from baseline PSA if there was no drop in PSA after starting treatment).

**8.2.2 Radiographic Skeletal progression on bone scan** is defined as 2 or more new lesions on radionuclide bone scans (PCWG2 criteria). Should two or more new bone lesions be evident at the first imaging assessment (at end of protocol specified therapy), two or more additional new lesions must be evident on a confirmatory assessment at least 6 weeks later.

A bone scan may be ordered at the discretion of the treating physician within the first 7 months of protocol treatment for symptoms e.g. bone pain. If new bone lesions appear in the absence of a rising PSA within the first 7 months of protocol treatment, the site investigator at the institution must consult the sponsor-investigator (via the HCRN Project Manager) to discuss the possibility of tumor flare.

For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

### **8.2.3 Radiographic Soft Tissue Progression per RECIST 1.1 Criteria (at least 1 of the following):**

Twenty percent increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm.

Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided).

Appearance of any new lesion/site.

Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions.

Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the subject could alter the size of the effusion.

### **8.2.4 Symptomatic Deterioration**

Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

### **8.3 Performance Status**

Subjects will be graded according to the ECOG Performance Status Scale. Please see Study Procedures Manual (SPM).

### **8.4 Two Year PSA Progression-Free Survival**

From date of randomization to first occurrence of PSA progression, symptomatic deterioration, or death due to any cause. Subjects without progression are censored at last date of contact.

### **8.5 PSA Response Categories**

- Undetectable PSA is defined as a PSA level of  $\leq 0.2$  ng/mL after seven cycles.
- A PSA partial response (PSA PR) after seven cycles is defined as a PSA that is between 0.2 and 4 ng/mL.

### **8.6 Time to Castration Resistance**

Castration resistant prostate cancer is defined as either PSA progression or radiographic progression. Time to Castration resistance will be counted from start of ADT (first LHRH agonist/antagonist/surgical castration) to development of castration resistance by either criterion:

- **PSA progression** per 10.2.1. Castration resistance will be determined to have occurred at the time of the first PSA increase.

- **Radiographic progression** Castration resistance will be determined to have occurred at the time of the first imaging assessment showing progression not the confirmatory scan (for bone lesions).

### **8.7 Time to Radiographic Progression**

Radiographic progression is defined by imaging (also see notes on PET). For soft tissue lesions, the smallest measurements recorded since the treatment started will be used as reference. For bone scans, the prior scan with least tumor burden scan in bone will be used as reference. Time to radiographic progression will be counted from randomization to radiographic progression.

### **8.8 Radiographic Progression-Free Survival**

Time to Radiographic progression or death, whichever occurs first, will be calculated for each subject. Subjects who do not have radiographic progression or death upon follow-up will be censored at their last radiographic assessment.

### **8.9 Symptomatic Skeletal Related Event (SSRE)**

Any of the following: Use of external beam radiotherapy (EBRT) to relieve skeletal related symptoms, new pathological vertebral and non-vertebral bone fractures, tumor related orthopedic surgical intervention, spinal cord compression.

### **8.10 Time to First SSRE**

From time of randomization to occurrence of first SSRE as defined in 10.10.

### **8.11 Alkaline Phosphatase End-Points**

The proportion of subjects with elevated ( $>ULN$ ) serum total alkaline phosphatase (ALP) at baseline who normalize their alkaline phosphatase ( $\leq ULN$ ) after 12 weeks of therapy, assess time to ALP progression (above ULN and  $\geq 25\%$  increase in ALP from baseline/nadir (whichever is lower)) will be determined.

### **8.12 Response Criteria for Soft Tissue Lesions; Evaluation of Target Lesions**

\*Complete Response (CR): Disappearance of all target lesions. All pathological lymph nodes must have decreased to  $<10mm$  in short axis.

\*Partial Response (PR): At least a 30% decrease in the sum of the 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 or the appearance of one or more new lesions

\*Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

### **8.13 Response Criteria for Soft Tissue Lesions; Evaluation of non-target lesions**

\*Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

\*Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

\*Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions\*

\*Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

#### 8.14 Evaluation of best soft tissue 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 PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target lesion	New Lesion	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective evidence of progression after discontinuation.

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

#### 8.15 Definitions for Soft Tissue Response Evaluation –RECIST version 1.1

##### First Documentation of Response:

The time between initiation of therapy and first documentation of PR or CR.

##### Confirmation of Response:

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

**Duration of Response:**

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

**Duration of Overall Complete Response:**

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

**Objective soft tissue response rate:**

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

## 9. EXPLORATORY CORRELATIVES

### 9.1 Bone Turnover Markers

Samples for bone turnover markers will be collected and stored until funding can be secured for the analyses described below.

Background and Specific Hypothesis:

Bone metabolism is distinguished by two activities - the formation of new bone by osteoblasts, and the resorption of old bone by osteoclasts. These processes are tightly coupled in space and time. Ultimately, bone mass is dependent upon the balance between formation and resorption. In prostate cancer, this homeostatic balance tips, such that osteoblastic activity predominates, resulting in sclerotic bone metastases. Bone metastasis is a very common event in subjects with prostate cancer and is a frequent source of morbidity, including bone pain or fracture. Many prostate cancer subjects with bone metastases have elevated circulating biochemical markers of bone metabolism, including markers for osteoblast and osteoclast activity. These serum-based biomarkers have been investigated as indicators of bone turnover for their potential as prognostic and/or predictive variables. Prior studies have suggested that elevated markers of bone turnover are strongly prognostic for poor survival in castration resistant prostate cancer subjects. However, their prognostic role in newly diagnosed (hormone-naïve) prostate cancer and their predictive value to help select those most likely to benefit from systemic therapy remain vexing clinical questions.

SWOG S0421 was a large placebo-controlled Phase III study of docetaxel with or without the endothelin antagonist atrasentan in castration resistant prostate cancer (CRPC) subjects with skeletal metastases. Disappointingly, no overall survival benefit was observed for the docetaxel/atrasentan arm. However, as a translational science component of that randomized trial SWOG prospectively assessed pre-treatment and serial serum markers of bone turnover to validate their prognostic and predictive value in these castration-resistant subjects. The SWOG study measured markers of bone resorption (N-telopeptide, NTX & Pyridinoline, PYD) and bone formation (C-terminal collagen propeptide, CACP & bone alkaline phosphatase, BAP). Cox regression models were developed for overall survival based on baseline BMB (log-2 scale),

adjusted for potentially confounding clinical variables (including PSA, bisphosphonate use, age, race, performance status, Gleason score, and pain score, among others). The study also explored the effect of treatment on bone marker levels in week 9 (as compared to baseline) and sought to find an association between a change in marker levels and overall survival outcomes. A Cox model was fit with main effects and Bone Marker x Treatment interaction; adjusted for clinical variables, to assess the predictive value of atrasentan on overall survival. Of 1,038 subjects enrolled in SWOG S0421, 855 (91%) had baseline serum submitted, of which 778 samples (75%) were usable and subsequently analyzed. The bone turnover values (median; range) were as follows: NTX (14 nM; 9.3-23.9), BAP (64.7 u/L; 35-164), CICP (9.5 ng/mL; 6.5-17.4), & PYD (2.8 nmol/L; 2.2-3.9).

Elevated markers of bone turnover (> median value) were prognostic for overall survival in SWOG 0421. Hazard ratios are reported for a 2-fold increase in markers. Follow-up analysis revealed that subjects with high marker levels (i.e., upper 25%-ile across all markers) not only have a very poor prognosis (HR = 4.3,  $p < 0.001$ ) but also appear to have a significant survival benefit from atrasentan (interaction-HR=0.33;  $p=0.002$ ), even with highly conservative statistical analysis including Bonferroni adjustment. There were 6% (47) of the 778 subjects with a complete set of measurements on baseline markers. The HR in the high marker group was estimated at 0.34 (95% CI: 0.13, 0.89); this compares with a HR of 1.04 (95% CI: 0.86, 1.25) in the low marker group.

There was also strong evidence for a significant association between the change in bone marker concentrations from baseline to Week 9 and overall survival for all bone markers. Presently, it is unclear whether these same observations will be observed in a somewhat different subject context: i.e., in the newly diagnosed, metastatic prostate cancer setting (non-castrate resistant).

Radium-223 dichloride demonstrated similar declines in bone turnover markers in CRPC including BAP in a phase 2 clinical trial in prostate cancer and in the randomized phase 3 trial<sup>11,12</sup>. The encouraging results from SWOG S0421 bone marker studies in CRPC and the proven effects of radium-223 dichloride on bone turnover lead us to pose several clinically relevant questions that can be prospectively explored in this study:

- Are markers of bone metabolism of prognostic and predictive value only in the CRPC setting, or do they have value in newly diagnosed metastatic prostate cancer?
- How will this radium-223 dichloride-induced bone phenotype behave in terms of response and survival when compared to a control group that is not receiving radium-223 dichloride?
- Can we use bone turnover biomarkers to explore who will benefit from radium-223 dichloride inhibitor therapy?

**We therefore hypothesize** that baseline levels of bone metabolism markers in sera collected from subjects with newly diagnosed metastatic prostate cancer will be of strong prognostic value and will also be predictive of benefit from radium-223 dichloride in combination with androgen deprivation therapy. A secondary hypothesis is that serial assessment of these same markers will demonstrate that lower marker levels at end of treatment visit will be associated with improved survival. To explore the effects of radium-223 dichloride on bone turnover in hormone naïve prostate cancer, serum markers of bone formation and bone resorption will be analyzed before,

during and after radium-223 dichloride treatment. Exploratory analyses will be performed to correlate the changes in bone turnover markers with clinical outcomes of interest.

These will be tested through the following **Specific Aims**:

- To measure levels of selected markers of bone formation and resorption in sera in subjects enrolled in this proposed randomized Phase II trial of ADT + radium-223 dichloride versus ADT alone in subjects with newly diagnosed subjects with metastatic prostate cancer.
- To correlate the results of these marker studies with PSA response, tumor response, progression-free survival (radiographic and PSA progression free survival), and overall survival to detect prognostic (baseline or pre-treatment sera) and/or predictive value (baseline biomarker x treatment interaction; serial sera).
- To identify prognostic groups based on baseline bone markers and other clinical and disease-related factors.

**Serum biomarkers of bone turnover** for bone resorption [N-telopeptide (NTX) expressed in nM Bone Collagen Equivalents, C-collagen fragments (CTX-I EIA) expressed in ng/mL] & formation [osteocalcin (OC) expressed in ng/mL & bone alkaline phosphatase (BAP) expressed in U/L] will be measured using commercially available assays from Quidel (OC, BAP), Immunodiagnostic Systems (IDS) (CTX-I) & Osteomark (NTX).

Due to the limited sample size in this Phase II setting, correlative studies will be considered exploratory in nature and no adjustments will be made for the multiple marker comparisons being explored. We could then attempt to validate hypotheses generated from this study in a subsequent phase III study.

**Bone Turnover Marker Correlative Study Design:**

Serial serum specimens will be submitted for the proposed correlative studies at the following time points:

- Pre-Dose on Day 1 of Cycle 1 (in the late induction group; for the early induction group, there will be no pre-treatment specimen)
- Thereafter on Day 1 of each Cycle (Cycle 2-Cycle 7) of protocol specified therapy for the following biomarkers: N-telopeptide (NTX), C-collagen fragments (CTX-I EIA), osteocalcin (OC) & bone alkaline phosphatase (BAP).
- At end of treatment visit.

Refer to the CLM for collection, labeling, processing and shipping instruction for the serum samples.

## **9.2 CTCs (Circulating Tumor Cells)**

The EPIC™ Sciences CTC platform will be used to detect and characterize the CTCs in this study. The platform utilizes no positive selection, allowing for enumeration and characterization of all CTCs including traditional CTCs (CK+, CD45- and morphologically distinct), epithelial mesenchymal transition (EMT) candidate CTCs (CK-, CD45-, and morphologically distinct) and small cell PCa (CK+, CD45-, morphologically similar to white blood cells). **We seek to**

**enumerate CTCs and detect evidence of radiation induced DNA double strand repair foci on CTCs.**

H2AX (H2A histone family, member X- a marker of DNA repair) becomes phosphorylated on serine 139, then called gamma-H2AX, as a reaction to DNA Double-strand breaks (DSB). The kinases of the PI3-family (Ataxia telangiectasia mutated, ATR and DNA-PKcs) are responsible for this phosphorylation, especially ATM. The modification can happen accidentally during replication fork collapse or during controlled physiological processes such as V(D)J recombination but also of relevance to the current study, in the response to ionizing radiation. Gamma-H2AX is a sensitive target for looking at DSBs in cells. The role of the phosphorylated form of the histone in DNA repair is under discussion but it is known that because of the modification the DNA becomes less condensed, potentially allowing space for the recruitment of proteins necessary during repair of DSBs. Mutagenesis experiments have shown that the modification is necessary for the proper formation of ionizing radiation induced foci in response to double strand breaks.

**Sample Collection and Handling:**

Blood samples from will be obtained at 3 time points and shipped to Epic Sciences (San Diego, CA) at ambient temperature.:

- C1D1 (late induction group only)
- C2D1 (early induction group only)
- C4D1
- EOT visit

**Blood sample preparation and storage:**

Red blood cells will be lysed and nucleated blood cells are dispensed onto glass microscope slides according to methods previously described<sup>13-15</sup> and placed at -80°C for long term storage at Epic Sciences. Up to 12 slides are prepared for each blood sample, each containing approximately 3 million nucleated cells, while the number of slides created from each individual sample is determined by the volume of blood received and the white blood cell (WBC) count. CTC slides stored at -80C using this approach are stable over 1 year (unpublished data).

**CTC identification and protein characterization:**

CTC analysis will be performed in batches. Two slides from each subject sample will be thawed, then subjected to an IF staining protocol to distinguish CTCs from WBCs as described previously<sup>13-15</sup>. In addition to DAPI, CD45, and cytokeratins, antibodies targeting gamma-H2AX will be utilized. Stained slides were then imaged on Pyxis™, a high speed imaging platform that images all 3M cells on each slide in less than 15 minutes. Captured images were analyzed by Atlas™ software that characterizes each cell by over 90 parameters including cell size, cell shape and marker intensities, then presents CTC candidates in an interactive report. All candidates were then reviewed by trained technicians, and CK+/CD45- cells with intact, DAPI+ nuclei exhibiting tumor-associated morphologies are classified as CTCs. Candidate CTCs as described are tracked and include CK-/CD45- cells with morphological distinction and/or AR positivity, CK+/CD45- small cells (morphologically similar or smaller to white blood cells), and apoptotic CTCs (identified by nuclear or cytoplasmic fragmentation). We will utilize our optimized immunofluorescence assay to detect phospho-ser139-H2AX otherwise known as gamma-H2AX.

Refer to the CLM for collection, labeling, processing and shipping instructions for the CTC samples.

### **9.3 Samples for future studies**

Subject consent will be obtained for additional samples collected for future studies. Hoosier Cancer Research Network will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network biorepository.

This includes:

- Whole blood: Mandatory
  - Whole blood will be collected prior to treatment on Cycle 1 Day 1 (late induction group) or Cycle 2 Day 1 (early induction group).
- Pre- and Post-treatment plasma: Mandatory
  - Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 (late induction group) or Cycle 2 Day 1 (early induction group) and at End of Treatment (both groups).
- Pre- and Post-treatment serum: Mandatory
  - Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 (late induction group) or Cycle 2 Day 1 (early induction group) and at End of Treatment (both groups).

Please refer to the CLM for all sample collection, processing, labeling and shipping instructions.

### **9.4 Assessment of Pain Level and Analgesic Use**

A key finding in the randomized phase III ALSYMPCA trial was the reduction in pain with radium-223 dichloride therapy. In the present study, subject-reported pain will be collected using standard paper surveys during clinic visits. Pain will be assessed by means of the Brief Pain Inventory Short Form (BPI-SF) questionnaire at baseline, on Cycle 4 Day 1 visit before dose and at the end of treatment visit. The worst pain recorded at each time point will be used as a numeric score for quantitative comparison across time points and between treatment arms. Analgesic use scores will be assigned by the treating physician according to the World Health Organization (WHO) scale at baseline, on Cycle 4 Day 1 visit before dose and at the end of treatment visit.

### **9.5 BPI-SF**

The severity of subject-reported pain and its impact on daily functions will be self-assessed by the study subjects using the Brief Pain Inventory-Short Form (BPI-SF) measure.<sup>16</sup> BPI-SF will be self-administered by the subject at Cycle 1 Day 1 of (Late Induction group) or Cycle 2 Day 1 (Early Induction group), Cycle 4 Day 1 and at end of treatment.

BPI-SF allows subjects to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function (*e.g.*, general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). BPI-SF is a 15-item, self-administered, clinically validated, reliable and responsive measure developed to assess pain related to cancer. The instrument is available in validated multilingual versions; on average, it requires less than 10 minutes to complete the questionnaire.

In this study, BPI-SF will be scored by worst pain recorded at each time point. Scores range from 0-10 and a higher score indicates a higher level of pain. The BPI-SF should be self-administered by the subject alone during his scheduled visit at the site. The instrument should be administered at the start of the visit, before the subject sees the physician so that any interaction between the subject and physician will not influence the subject's responses to the questionnaire. The questionnaire should also be administered before the subject is asked about adverse experiences and concurrent illnesses, again so that any discussions of health problems do not influence the subject's responses. A quiet place should be provided for the subject to complete the BPI-SF. It is important that the subject completes the BPI-SF alone, without any advice from family members or friends who may accompany them.

How should the Questionnaire be introduced? A sample script for introducing the questionnaire is given below.

“Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, please complete this questionnaire about your health. The questionnaire is easy to fill out. The instructions are on the front cover (point to them). You should read each question and then circle the appropriate number that matches your answer. Remember that this is not a test and there are no right or wrong answers. Choose the answer that best describes the way you feel. I will quickly review the questionnaire when you are done to make sure that all the questions have been answered. You should answer these questions by yourself. Your spouse or other family members should not help you when you answer the questionnaire. I will be nearby in case you want to ask me any questions. Please return, the questionnaire to me when you have finished”.

What to do if the subject asks for clarification?

Some subjects may ask the meaning of specific questions. If this happens, the staff member can assist the subject by re-reading the question for them verbatim. If the subject asks what something means, do not try to explain what the question means, but tactfully suggest that the subject use his own interpretation of the question. All subjects should answer the questions based on what they think the questions mean, or the study results may be biased.

Questionnaire completion:

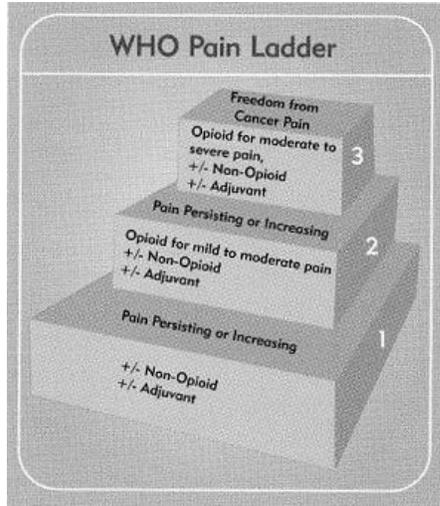
When the subject returns the questionnaire, check that all of the questions have been answered. If the questionnaire is not complete, point out to the subject that some of the questions were not answered. If the subject does not quickly volunteer to answer these items, ask him whether he had any difficulty completing the questionnaire. If the subject says that he had trouble understanding a question, ask him why he had difficulty with that item. Re-read the question for him verbatim, but do not attempt to explain or reword the question, as explained before. If the subject is still unable to answer the question, accept the questionnaire as is.

Some subjects may be confused by the response choices. They may want to respond with “I don't know” or some other response choice that is not available. If this happens, try to help the subject choose one of the response categories by saying something like: “I know that it may be difficult for you to choose an answer, but which of these answers do you think comes closest to the way that you are thinking or feeling?” If the subject still cannot select an answer, accept the questionnaire as is. Occasionally, subjects may not report having difficulty with a question or the

response choices, but still may hesitate or refuse to answer an item or items. If this happens, accept the questionnaire as is. If a subject asks for interpretation of his responses or asks for his scores on the questionnaire, tell him that you are not trained to score or interpret the questionnaire. Emphasize that their answers will be kept confidential.

Completed questionnaire: Thank the subject once he has completed the questionnaires and you have checked them for completeness.

B. WHO Ladder scale:



WHO Score	Description	Opioid Use
0	No pain	
1	Mild pain	using non-opioid +/- adjuvant daily on average
2	Moderate pain	using weak opioid +/- non-opioid +/- adjuvant daily on average. Weak opioids include codeine phosphate, dextropropoxyphene, dihydrocodeine or tramadol.
3	Severe pain	Strong opioid +/- non-opioid +/- adjuvant daily on average. Strong opioids include morphine, oxycodone, fentanyl, buprenorphine, oxymorphone, hydromorphone.

The WHO ladder score will be assigned by the treating physician based on the subject’s daily analgesic use on average. Score will be assigned pre-treatment on Cycle 1 Day 1 of (Late Induction group) or Cycle 2 Day 1 (Early Induction group), Cycle 4 Day 1 and at end of study visit. At each time-point, a single numeric score (0, 1, 2 or 3) will be assigned based on the scale as above.

## 10 DRUG INFORMATION

For this study, bicalutamide, degarelix, goserelin acetate and leuprolide acetate are commercially available; therefore, Prescribing Information will be used. Radium-223 dichloride will be supplied for this study by Bayer Pharmaceuticals but the product insert for radium-223 dichloride is freely available as radium-223 dichloride is regulatory approved in castration resistant prostate cancer. Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

### 10.1 Radium-223 dichloride (Xofigo™)

#### Pharmacology

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

#### Pharmacokinetics

The pharmacokinetics of radium-223 dichloride in blood was linear in terms of dose proportionality and time independence in the dose range investigated (51 to 276 kBq [1.4 to 7.5 microcurie]).

**Distribution:** After intravenous injection, radium-223 is rapidly cleared from the blood and is distributed primarily into bone or is excreted into intestine. Fifteen minutes post-injection, about 20% of the injected radioactivity remained in blood. At 4 hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours after the injection. At 10 minutes post-injection, radioactivity was observed in bone and in intestine. At 4 hours post-injection, the percentage of the radioactive dose present in bone and intestine was approximately 61% and 49%, respectively. No significant uptake was seen in other organs such as heart, liver, kidneys, urinary bladder, and spleen at 4 hours post-injection.

**Metabolism:** Radium-223 is a radioactive isotope that decays and is not metabolized. Radium-223 has a physical half-life of 11.4 days.

**Elimination:** Excretion in urine is minimal and there is no evidence of hepato-biliary excretion. The major route of elimination is feces.

#### Adverse Events

In the placebo-controlled phase 3 randomized clinical trial ALSYMPCA<sup>12</sup> in subjects with metastatic castration-resistant prostate cancer with bone metastases, 600 subjects received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Radium-223 dichloride and best standard of care and 301 subjects received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of subjects had received docetaxel in the Radium-223 dichloride and placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Radium-223 dichloride and 18 weeks (5 cycles) for placebo. The

most common adverse reactions ( $\geq 10\%$ ) in subjects receiving radium-223 dichloride were nausea, diarrhea, vomiting, and peripheral edema. Grade 3 and 4 adverse events were reported among 57% of Radium-223 dichloride-treated subjects and 63% of placebo-treated subjects.

The most common hematologic laboratory abnormalities in Radium-223 dichloride-treated subjects ( $\geq 10\%$ ) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Treatment discontinuations due to adverse events occurred in 17% of subjects who received Radium-223 dichloride and 21% of subjects who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Radium-223 dichloride were anemia (2%) and thrombocytopenia (2%).

Adverse Events with Possible Relationship to Radium-223 dichloride		
Likely (>20%)	Less Likely ( $\leq 20\%$ )	Rare but Serious (<3%)
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>		
Anemia	Neutropenia	
Lymphocytopenia	Pancytopenia	
Leukopenia		
Thrombocytopenia		
<b>GASTROINTESTINAL DISORDERS</b>		
Nausea		
Diarrhea		
Vomiting		
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>		
	Peripheral edema	
<b>RENAL AND URINARY DISORDERS</b>		
	Renal failure and impairment	

### Dosimetry

The absorbed radiation doses in major organs were calculated based on clinical biodistribution data in five subjects with castration resistant prostate cancer. Calculations of absorbed radiation doses were performed using OLINDA/EXM (Organ Level Internal Dose Assessment/EXponential Modeling), a software program based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, which is primarily an alpha particle-emitter, assumptions were made for intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations for Radium-223 dichloride, considering its observed biodistribution and specific characteristics.

### Special Populations

**Pregnancy and Lactation:** Radium-223 dichloride is categorized as Category X. Radium-223 dichloride can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of Radium-223 dichloride in pregnancy and Radium-223 dichloride is not indicated for use in women, maternal use of a radioactive therapeutic agent could affect development of a fetus. Radium-223 dichloride is contraindicated in women who are or may become pregnant while receiving the drug. If this drug

is used during pregnancy, or if the subject becomes pregnant while taking this drug, apprise the subject of the potential hazard to the fetus and the potential risk for pregnancy loss.

**Geriatric Use:** Of the 600 subjects treated with Radium-223 dichloride in the randomized trial, 75% were 65 years of age and over and while 33% were 75 years of age and over. No dosage adjustment is considered necessary in elderly subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

**Subjects with Hepatic Impairment:** No dedicated hepatic impairment trial for Radium-223 dichloride has been conducted. Since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is unlikely to affect the pharmacokinetics of radium-223 chloride. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in subjects with mild hepatic impairment. No dose adjustments can be recommended for subjects with moderate or severe hepatic impairment due to lack of clinical data.

**Subjects with Renal Impairment:** No dedicated renal impairment trial for Radium-223 dichloride has been conducted. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in subjects with existing mild (creatinine clearance [CrCl] 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for subjects with severe renal impairment (CrCl less than 30 mL/min) due to limited data available (n = 2).

**Males of Reproductive Potential:** Because of potential effects on spermatogenesis associated with radiation, men who are sexually active are advised to use condoms and their female partners of reproductive potential to use a highly effective contraceptive method during and for 6 months after completing treatment with Radium-223 dichloride.

**Drug Interactions:** No formal clinical drug interaction studies have been performed. Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Radium-223 dichloride in the randomized clinical trial.

### **Dosing and Administration**

- The volume to be administered to a given subject should be calculated using the:
- Subject's most recent (within 4 weeks) body weight (kg)
- Current Dosage level 55 kBq/kg body weight (or 1.5 microcurie/kg body weight)
- Radioactivity concentration of the product (1,100kBq/ml; 30 microcurie/ml at the reference date)
- Decay correction factor to correct for physical decay of radium-223 (see table below)

**Decay Correction Factor Table**

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

The Decay Correction Factor Table is corrected to 12 noon Central Standard Time (CST). To determine the decay correction factor, count the number before (-1 to -14) or after (1 to 14) the reference date. The Decay Correction Factor Table includes a correction to account for the 7 hour time difference between 12 noon European Time (CET) at the site of manufacture and 12 noon US CST, which is 7 hours earlier than CET.

The current total volume to be administered to a subject is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 55 \text{ kBq/kg body weight (1.5 microcurie/kg body weight)}}{\text{Decay factor} \times 1,100 \text{ kBq/mL (30 microcurie/ml)}}$$

**Instructions for Use / Handling**

General warning: Radium-223 dichloride (an alpha particle-emitting pharmaceutical) should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal of Radium-223 dichloride are subject to the regulations and/or appropriate licenses of the competent official organization.

Radium-223 dichloride should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. Radiation protection: The administration of Radium-223 dichloride is associated with potential risks to other persons (e.g., medical staff, caregivers and subject’s household members) from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. 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.

For drug handling: Follow the normal institutional 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 and profusely with water. In the event of spillage of Radium-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-diamine-tetra acetic acid (EDTA) solution is recommended to remove contamination.

For subject care: Whenever possible, subjects 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-223 dichloride or subject fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of subject doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 microcurie). In keeping with the As Low As Reasonably Achievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughter molecules allows for the radioactivity measurement of Radium-223 dichloride and the detection of contamination with standard instruments.

Dose handling: The Radium Ra 223 dichloride vials must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production. Radium Ra 223 dichloride is an alpha-pharmaceutical and should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides. One dedicated person and a back-up designee will have responsibility as assigned from the site investigator for handling and storage of Radium Ra 223 dichloride. All administrations of Radium Ra 223 dichloride are based on the certified activity of Radium Ra 223 dichloride at the calibration date.

1. Instructions for preparation: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Radium-223 dichloride is a ready-to-use solution and should not be diluted or mixed with any solutions. Each vial is for single use only.

2. Administration: Radium-223 dichloride is administered by slow intravenous injection over 1 minute. The intravenous access line or cannula should be flushed with isotonic saline before and after injection of radium-223 dichloride.
3. Updated SRM: upon notification by Bayer each center is required to update the dial settings to correspond to the new NIST standard). The current dial settings are to remain in effect until Bayer obtains FULL approval from the FDA for implementation. In preparation for implementation of the NEW dial setting, the clinical study center will receive a sealed vial labeled NIST standard containing a Radium Ra 223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. The amount of Radium Ra 223 dichloride in the vial will be stated on the label. Instructions for the dial setting, including the calibration log form, will be enclosed with the dispatch of the calibration sample. All sites will be notified by Bayer when FINAL regulatory approval from the FDA is in place and the updated NIST standardization is to be implemented.

### **Storage and Stability**

Storage: Store at room temperature, below 40° C (104° F). Store Radium-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. Follow procedures for proper handling and disposal of radioactive pharmaceuticals

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

### **How Supplied**

The alpha-pharmaceutical Radium Ra 223 dichloride is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of Radium Ra 223 dichloride ( $^{223}\text{RaCl}_2$ ) for IV administration. It should not be diluted or mixed with any solutions. Each vial for a single use only.

Radium Ra 223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0-8.0. The radioactive concentration at the reference date is 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.

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

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.

## 10.2 Bicalutamide (Casodex®) (NSC-722665)

### Description

Bicalutamide is a racemic mixture containing two enantiomers, (2RS)-4'-Cyano-3(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-trifluoromethyl) propionanilide.

Bicalutamide is an active non-steroidal antiandrogen and its antiandrogen activity resides exclusively in the (-) or (R) enantiomer. Unlike flutamide, it is peripherally selective and does not cause a rise in serum LH or Testosterone in male rats and dogs. This peripheral selectivity may be because it penetrates poorly the CNS and Hypothalamus (the site of negative feedback of androgens). In humans, rises in LH, Testosterone and Estradiol concentrations were seen. These rises were not dose related. In 90%, testosterone levels remained within normal limits. There was no significant rise in mean serum FSH.

### Toxicology

In rats, besides antiandrogenic changes, there was evidence of hepatocyte hypertrophy and basophilia. In dogs treated for 6 months, there was increased heart rate with decreased PR interval, transient decrease in circulating PMNs and increased plasma cholesterol. No cardiac pathology was found. In a mouse oncogenicity study, an increased incidence of hepatocellular carcinoma was observed in the top dose male group (75 mg/kg/day). The no effect dose level for hepatocellular carcinoma in this study was 15 mg/kg/day with steady state blood levels in excess of 10 µg/ml. The mechanism for this tumor formation is a non-genotoxic, phenobarbitone-type MFO induction and is not considered to represent a risk for humans. A two-year study in rats and female mice at similar doses did not show an increased incidence of hepatic tumors.

Bicalutamide has been given to over 3,500 men in 35 different clinical studies worldwide, in doses up to 600 mg daily. When bicalutamide is given in combination with an LHRH analogue, the pharmacologic adverse event profile is dominated by the LHRH analogue and includes hot flashes (53%), gynecomastia (9%) and breast pain (6%). Other adverse events reported regardless of causality included diarrhea (12%), constipation (22%), nausea (15%) and abdominal pain (11%). Other adverse events were reported, such as fatigue (22%), pain (35%), back pain (25%), pelvic pain (21%), infection (18%), peripheral edema (13%), dyspnea (13%), nocturia (12%), hematuria (12%), anemia (11%), and dizziness (10%). Bicalutamide has been associated with changes in liver function, although these are infrequent (7%) and rarely occur with jaundice. Many of these changes improved or resolved despite continuation of bicalutamide therapy. There have been no reports of fatal hepatotoxicity associated with bicalutamide therapy.

### Pharmacology

Pharmacokinetics: Animal studies: After oral single dose administration, absorption of the compound was slow with peak concentration occurring 3 - 12 hours and plateau between 2 and 48 hours. There was non-proportional increase in plasma levels with increasing doses.

Elimination half-life ranges from 17 - 28 hours in male rats, 21 - 29 hours in female rats and 5 - 7.5 days in dogs. 91 - 96% of bicalutamide is bound to plasma protein.

Human studies: After single doses, mean time for peak plasma concentration was 6 hours at 10 and 30 mg, but at 50 mg, it was 16 hours. Mean plasma elimination half -lives after 12 weeks of 10, 30, 50, 100 mg/day was 7 - 10 days. This finding was consistent with single dose data. In subjects given daily doses of 50 mg, mean plasma concentration was 10 ug/ml at 12 weeks. After single doses, there was linear increase with doses between 10 and 50 mg, but became non-linear at doses of 50 - 100 mg. At 100 mg, the oral bioavailability is reduced by 30% but plasma elimination half -life is unchanged. Bicalutamide is extensively metabolized and metabolites are excreted by both the biliary and urinary system.

Formulation: Bicalutamide is prepared as round, film-coated green or white tablets containing standard recipients and 50 mg of the drug.

Storage and stability: All packages of bicalutamide should be stored securely in a dry place at room temperature.

Route of Administration: Bicalutamide is to be administered in tablet form as a once-daily oral dose. Subjects should be instructed to take one tablet once daily.

Supplier: Bicalutamide is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the study. Please refer to the Physician Desk Reference and package insert for complete information.

Common side effects include:

- hot flashes, or short periods of feeling warm and sweating whole body pain in your back, pelvis, stomach
- feeling weak
- constipation
- Infection
- nausea
- swelling in your ankles, legs or feet
- diarrhea
- blood in your urine
- waking from sleep to urinate at night
- a decrease in red blood cells (anemia)
- feeling dizzy

Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

### 10.3 Degarelix (Firmagon<sup>®</sup>)

#### Description

DEGARELIX is a sterile lyophilized powder for injection containing degarelix (as the acetate) and mannitol. Degarelix is a synthetic linear decapeptide amide containing seven unnatural amino acids, five of which are D-amino acids. The acetate salt of degarelix is a white to off-white amorphous powder of low density as obtained after lyophilization.

The chemical name of degarelix is D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-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-(1-methylethyl)-L-lysyl-L-prolyl. It has an empirical formula of C<sub>82</sub>H<sub>103</sub>N<sub>18</sub>O<sub>16</sub>Cl and a molecular weight of 1632.3 Da.

DEGARELIX delivers degarelix acetate, equivalent to 120 mg of degarelix for the starting dose, and 80 mg of degarelix for the maintenance dose. The 80 mg vial contains 200 mg mannitol and the 120 mg vial contains 150 mg mannitol. DEGARELIX is for subcutaneous administration only.

#### Dosing and Administration

DEGARELIX is administered as a subcutaneous injection in the abdominal region. As with other drugs administered by subcutaneous injection, the injection site should vary periodically. Injections should be given in areas of the abdomen that will not be exposed to pressure, e.g., not close to waistband or belt nor close to the ribs.

DEGARELIX is supplied as a powder to be reconstituted with Sterile Water for Injection, USP (WFI). Reconstituted drug must be administered within one hour after addition of Sterile Water for Injection, USP. Do not shake the vials. The instruction for reconstitution needs to be carefully followed. Administration of other concentrations is not recommended. See package insert for full reconstitution and administration instructions.

#### How Supplied

Starting dose: One starting dose comprises 240 mg given as two 3 mL injections of 120 mg each.

Powder for injection 120 mg:

One vial of DEGARELIX 120 mg contains 120 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 3 mL of Sterile Water for Injection. 3 mL is withdrawn to deliver 120 mg degarelix at a concentration of 40 mg/mL.

Maintenance dose: One maintenance dose comprises 80 mg given as one 4 mL injection.

Powder for injection 80 mg:

One vial of DEGARELIX 80 mg contains 80 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 4.2 mL of Sterile Water for Injection. 4 mL is withdrawn to deliver 80 mg degarelix at a concentration of 20 mg/mL.

### **Storage and Stability**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Caution should be exercised in handling and preparing the solution of DEGARELIX. Several guidelines on proper handling and disposal of anticancer drugs have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling DEGARELIX. If DEGARELIX solution contacts the skin, immediately wash the skin thoroughly with soap and water. If DEGARELIX contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

### **Clinical Pharmacology**

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

A single dose of 240 mg DEGARELIX causes a decrease in the plasma concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and subsequently testosterone.

DEGARELIX is effective in achieving and maintaining testosterone suppression below the castration level of 50 ng/dL.

**Pharmacokinetics:** DEGARELIX forms a depot upon subcutaneous administration, from which degarelix is released to the circulation. Following administration of DEGARELIX 240 mg at a product concentration of 40 mg/mL, the mean C<sub>max</sub> was 26.2 ng/mL (coefficient of variation, CV 83%) and the mean AUC was 1054 ng•day/mL (CV 35%). Typically, C<sub>max</sub> occurred within 2 days after subcutaneous administration. In prostate cancer subjects at a product concentration of 40 mg/mL, the pharmacokinetics of degarelix were linear over a dose range of 120 to 240 mg. The pharmacokinetic behavior of the drug is strongly influenced by its concentration in the injection solution.

The distribution volume of degarelix after intravenous (> 1 L/kg) or subcutaneous administration (> 1000L) indicates that degarelix is distributed throughout total body water. In vitro plasma protein binding of degarelix is estimated to be approximately 90%.

Degarelix is subject to peptide hydrolysis during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the feces. No quantitatively significant metabolites were detected in plasma samples after subcutaneous administration. In vitro studies have shown that degarelix is not a substrate, inducer or inhibitor of the CYP450 or p-glycoprotein transporter systems.

**Excretion:** Following subcutaneous administration of 240 mg DEGARELIX at a concentration of 40 mg/mL to prostate cancer subjects, degarelix is eliminated in a biphasic fashion, with a median terminal half-life of approximately 53 days. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the DEGARELIX depot formed at the injection site(s). Approximately 20-30% of a given dose of degarelix was renally excreted, suggesting that approximately 70-80% is excreted via the hepato-biliary system in

humans. Following subcutaneous administration of degarelix to prostate cancer subjects, the clearance is approximately 9 L/hr.

There was no effect of age, weight or race on the degarelix pharmacokinetic parameters or testosterone concentration.

Common side effects include:

- hot flashes
- injection site pain, redness, and swelling, especially with the first dose
- weight gain
- increase in some liver enzymes
- tiredness
- hypertension
- back and joint pain
- chills
- urinary tract infection
- decreased sex drive and trouble with erectile function (impotence)

Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

#### **10.4 Goserelin acetate implant (Zoladex®) (NSC-606864)**

##### **Pharmacology**

Mechanism of Action: Following initial administration in males, goserelin causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of goserelin leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy.

In females, a similar down-regulation of the pituitary gland by chronic exposure to goserelin leads to suppression of gonadotropin secretion, a decrease in serum estradiol levels consistent with the postmenopausal state, and would be expected to lead to a reduction in ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone responsive tumors, if present. Serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration; however, after suppression was attained, isolated elevations of estradiol were seen in 10% of the subjects enrolled in clinical trials. Serum LH and FSH are suppressed to follicular phase levels within four weeks after initial administration of drug and are usually maintained at that range with continued use of goserelin.

##### **Pharmacokinetics**

1. Absorption: Goserelin 3.6 mg is released slowly in first 8 days, and then rapid and continuous release for the remainder of the 28-day dosing period. Time to peak concentration for goserelin 3.6 mg is 12-15 days in males and 8-22 days in females. Goserelin 10.8 mg

exhibits an initial rapid release resulting in a peak concentration at 2 hours after dosing. From Day 4 until the end of the 12-week dosing interval, the sustained release of goserelin produces a reasonably stable systemic exposure.

2. Distribution: Apparent volumes of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. Goserelin is approximately 27% protein bound.
3. Metabolism: Metabolism of goserelin by hydrolysis of the C-terminal amino acids is the major clearance mechanism. The half-life elimination ( $t_{1/2}$ ) is approximately 4 hours in males and 2 hours in females.
4. Elimination: Clearance of goserelin is very rapid and occurs primarily via urinary excretion (>90%; 20% as unchanged drug).

### **Dosing and Administration**

Goserelin is administered subcutaneously into the anterior abdominal wall below the navel line using aseptic technique.

### **Storage and Stability**

Refer to the current FDA-approved package insert for storage, stability and special handling information.

### **How Supplied**

1. Goserelin acetate implant is available in a 3.6 mg or 10.8 mg disposable syringe device. The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.
2. Goserelin is commercially available and will not be supplied by the study. Refer to the current FDA-approved package insert for additional information.

### **Common side effects**

- Problems getting an erection (impotence)
- Hot flushes and sweats
- Lowered interest in having sex (low libido)
- Temporary bruising and sore skin where you have the injection
- Breast tenderness and swelling

Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

## **10.5 Leuprolide (Eligard®, Lupron Depot®) (NSC-377526)**

### **Pharmacology**

Mechanism of Action: Leuprolide inhibits gonadotropin secretion by acting as a luteinizing hormone-releasing hormone (LHRH) agonist. Continuous administration results in suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. In males, testosterone levels are reduced to below castrate levels. Leuprolide may also act directly on the testes as well as act by a different mechanism not directly related to reduction in serum testosterone.

### **Pharmacokinetics**

1. Absorption: After the initial increase of leuprolide following each injection, mean serum concentrations remain relatively constant.
2. Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.
3. Metabolism: Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M-I) metabolite.
4. Elimination: Less than 5% of the leuprolide dose was recovered as parent and M-I metabolite in the urine following the 3.5 mg depot injection.

### **Dosing and Administration**

Leuprolide is administered intramuscular (Lupron Depot®) or subcutaneous (Eligard®) injection based on commercial depot formulation. Injection sites should be varied periodically.

### **Storage and Stability**

Refer to the current FDA-approved package insert for storage, stability and special handling information.

### **How Supplied**

Leuprolide acetate is available in 3.75 mg, 7.5 mg, 11.25 mg, 22.5 mg, 30mg, or 45 mg depot formulation kit with accompanying diluent. The prefilled dual chamber syringe contains lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid polymer.

Leuprolide is commercially available and will not be supplied by this study. Refer to the current FDA-approved package insert for additional information.

### **Common side effects include:**

- arm, back, or jaw pain
- bloody or cloudy urine
- blurred vision
- burning while urinating
- chest pain or discomfort
- chest tightness or heaviness
- difficult or labored breathing
- difficult, burning, or painful urination
- difficulty with moving
- dizziness
- frequent urge to urinate
- headache
- increased urge to urinate during the night
- muscle pain or stiffness
- nausea
- nervousness

- pain in the joints
- pale skin
- pounding in the ears
- slow or fast heartbeat
- sweating
- troubled breathing with exertion
- unusual bleeding or bruising
- unusual tiredness or weakness
- waking to urinate at night

Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions

## **11 ADVERSE EVENTS**

### **11.1 Definitions of Adverse Events**

#### **11.1.1 Adverse Event (AE):**

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. An adverse event may include the following: an adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug withdrawal and any failure of expected pharmacological action.

#### **11.1.2 Serious Adverse Event (SAE):**

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria:

- Results in death, other than death related to disease progression
- Is life-threatening.
  - The term ‘life-threatening’ in the definition refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
    - The admission results in a hospital stay of less than 24 hours.
    - The admission is pre-planned.  
(i.e. elective or scheduled surgery arranged prior to the start of the study)
    - The admission is not associated with an AE (e.g. social hospitalization for purposes of respite care).
    - However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of ‘medically important’ and as such may be reportable as an SAE

dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

- Results in persistent or significant disability/incapacity.
  - Disability means a substantial disruption of a person's ability to conduct normal life's functions.
- Is a congenital anomaly / birth defect.
- Is another medically important serious event.
  - An event may be considered an important medical event when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

### **11.1.3 Adverse Drug Reaction**

Adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### **11.1.4 Serious Adverse Drug Reaction**

A serious adverse drug reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drugs.

## **11.2 Adverse Event (AE) Reporting**

### **11.2.1 Site Requirements for Recording Adverse Events**

Adverse events (AEs) will be recorded from the time of consent and for 30 days after the last dose of study drugs, regardless of whether or not the event(s) are considered related to the study drugs. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be utilized for AE reporting. A copy of the CTCAE v4 can be downloaded from the CTEP website at <http://ctep.cancer.gov>.

All AEs considered related to study drug will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

### **11.2.2 Site Requirements for Reporting Serious Adverse Events to HCRN**

Site investigators and other site personnel must report any SAEs occurring from the time of informed consent to 30 days after the last dose of study drugs. This includes events both related and unrelated to the study drugs.

The definition of “related” being that there is a reasonable possibility the drug caused the adverse experience.

<b>Unrelated</b>	The Adverse Event is <i>clearly not related</i> to the study drug(s)
<b>Unlikely</b>	The Adverse Event is <i>doubtfully related</i> to the study drug (s)
<b>Possible</b>	The Adverse Event <i>may be related</i> to the study drug (s)
<b>Probable</b>	The Adverse Event is <i>likely related</i> to the study drug (s)
<b>Definite</b>	The Adverse Event is <i>clearly related</i> to the study drug (s)

The completed SAE Submission Form must be sent to HCRN **within 24 hours** of discovery of the event. The form may be sent to HCRN either electronically to [safety@hoosercancer.org](mailto:safety@hoosercancer.org) or by fax to 317-921-2053. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. The original copy of the SAE Submission Form and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information should be submitted to HCRN either electronically to [safety@hoosercancer.org](mailto:safety@hoosercancer.org) or by fax to 317-921-2053, using a SAE Submission Form stating that this is a follow-up to the previously reported SAE and providing the follow-up number if appropriate. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the subject continued or withdrew from study participation.

### 11.2.3 HCRN Requirements for Reporting Serious Adverse Events to Bayer

HCRN will report all SAEs to Bayer **within 24 hours** of receipt of the SAE Submission Form from the site and to regulatory authorities (FDA) per federal guidelines.

HCRN will report SAEs using a MedWatch form available at <http://www.fda.gov/medwatch/> for SAEs reportable to FDA; all other SAEs will be reported using the HCRN SAE Submission Form. All SAE reports must include the following minimum information:

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

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

- The date of onset
- The severity
- The time from administration of study drug(s) to start of the event
- The duration and outcome of the event
- Any possible etiology for the event
- The final diagnosis or syndrome, if known
- Action(s) taken, if any

All reports shall be sent electronically to:

**Electronic Mailbox:** [DrugSafety.GPV.US@bayer.com](mailto:DrugSafety.GPV.US@bayer.com)  
**Facsimile:** (973) 709-2185  
**Address:** Global Pharmacovigilance - USA  
**Mail only:** Bayer HealthCare  
P.O. Box 915  
Whippany, NJ 07981-0915

**Address:** **100 Bayer Boulevard, Whippany, NJ 07981**  
**FDX or UPS only** **67 Whippany Road, Whippany NJ 07981 for UPS**

**Reports for all Bayer products can also be phoned in via Bayer's Medical Communications Department**

Phone: 1-888-842-2937

#### **11.2.4 Expedited Reporting of Other Safety Information:**

Sites will report to HCRN **within 24 hours** of discovery of event and HCRN shall report to Bayer **within 24 hours** of receipt of report:

- An adverse event related to study specific procedures which the site investigator reasonably believes impacts subject safety (For Non-SAEs: site investigator decision whether to file to Bayer and other regulatory authorities).
- Any new and important event related to treatment with the study drug(s) which the site investigator reasonably believes impacts subject safety (this is up to the site investigator to determine what is new and important and related to the study drug. Site investigator decision whether to file to Bayer and other regulatory authorities).
- Any pregnancy during which a female patient was exposed to the study drug(s). Any pregnancy in the partner of a male subject, where the male subject was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).

Any communication, other than communication provided by Bayer, concerning safety related information to regulatory authorities or ethics committees including but not limited to:

Development Safety Update Reports (DSUR) / relevant parts of IND reports for study drugs.  
Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees.

#### **11.2.5 Sponsor-Investigator Responsibilities**

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

#### **11.2.6 HCRN Reporting to the Food and Drug Administration (FDA)**

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to Bayer's parent IND at time of submission.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report.

#### **11.2.7 IND Safety Reports Unrelated to this Trial**

Bayer will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via OnCore®.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

## **12. STATISTICAL CONSIDERATIONS**

### **12.1 Study Design**

Newly diagnosed metastatic prostate cancer subjects with  $\geq 2$  bone metastases will be accrued and randomized 1:2 to ADT without or with Radium-223 dichloride respectively. The primary aim of the study is to determine if the addition of Radium-223 dichloride to ADT will improve efficacy in this prostate cancer population. The primary efficacy endpoint is radiographic progression-free survival (rPFS). We expect the control arm with ADT alone to have a 12 month median rPFS. The addition of radium-223 to ADT will target an improvement of 7 months for a median rPFS of 19 months. A total of 140 events are required for at least 90% power to detect Hazard Ratio of 0.632 with a one-sided alpha of 0.1. The study powering is based on assumptions of 19 months median rPFS in the experimental arm and 12 months median rPFS in the control arm. Assuming exponential time to event data, a yearly dropout rate of 10% with

accrual in 24 months and study duration of 48 months, 204 subjects will provide 90% power with a 10% one-sided type I error. Hypothesis testing for the primary endpoint will be conducted at a one-sided 0.10 significance level using a stratified log-rank test. Randomization of 68 subjects to the ADT arm and 136 subjects to the ADT+R arm will be completed with stratification by extent of disease (<6 skeletal metastases without visceral disease versus  $\geq 6$  skeletal metastases or visceral disease) and baseline alkaline phosphatase (normal versus abnormal), abnormal alkaline phosphatase defined as  $> 130$  IU/L. If time anticipated for the number of events required for analysis significantly exceeds 48 months, the sponsor may enroll additional subjects to reach required number of events.

## 12.2 General Considerations

This is a randomized phase II study to assess the efficacy of ADT with Radium-223 dichloride compared to ADT alone in newly diagnosed metastatic prostate cancer subjects with bone metastases.

## 12.3 Interim Analysis

An interim analysis of safety is planned after treatment of 51 safety evaluable subjects. If probably or definitely related (attribution = probably, or definitely) SAE proportion is 40% or greater in ADT+R arm compared to the ADT arm then reassessment of dose in combination will be adjusted by lowering radium-223 dose to 27.5 kBq/Kg/dose for subsequent subjects<sup>17</sup>.

In addition, at 24 months, assessment of the number of events will be completed, blind to the arm of treatment. If time anticipated for the number of events required for analysis significantly exceeds 48 months, the study may enroll additional subjects to reach the required number of events.

## 12.4 Analysis Datasets

### Methods of Statistical Analysis

The definitions of the study populations are listed below.

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Intention-to-treat (ITT)	This will comprise all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment. (See Intent-To-Treat principle below).

Population	Definition
Per Protocol Set	This will comprise all subjects who received ADT or ADT+R for 1 cycle and have a radiographic assessment post-baseline.
Safety	All subjects who receive 1 dose of treatment will be included in the safety population.
Treated	This will comprise all subjects who have been exposed to the planned course of treatment to any extent.
ALP normalization	Subjects with abnormal ALP at baseline and at least one other post-baseline ALP measure.

Intention-To-Treat Principle - The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

### 12.5 Sample Size/Accrual/Study Duration/Replacement Rules

The sample size is 204 eligible and safety evaluable subjects. Accrual of 204 eligible and safety evaluable subjects is expected to take 24 months. Subjects will be followed for 2 years or until the last enrolled subject has progressed, died, has been followed for 24 months, or study is terminated, whichever occurs first. Subjects who are enrolled but do not receive any treatment will be replaced.

### 12.6 Analysis of Primary Objective

Subjects will be assessed for radiographic progression as described in section 8. Time from first dose of ADT to radiographic progression or death, whichever occurs first, will be calculated for each subject. For subjects who discontinue study treatment due to reasons other than death or investigator assessed progression, every effort will be made to continue tumor assessments on schedule until radiographic progressive disease or subject death. Subjects who do not have radiographic progression or death will be censored at their last measure for radiographic progression. The primary hypothesis test will be conducted at a one-sided 0.1 significance level using a stratified log-rank test. Kaplan-Meier methods will be used to report rPFS graphically by arm including the median rPFS and 12 and 24 month rPFS proportions in the ITT population. The log-rank test without stratification will be used as a sensitivity analysis.

### 12.7 Analysis of Secondary Objectives

Toxicity will be described within each arm by type, maximum grade and frequency among the safety population. The proportion of subjects in each arm with skeletal related events and secondary neoplasms will be reported individually and a mid p-value test will compare the proportions between arms.

Time to castration resistance (TTCR), PSA progression free survival (PCWG2 criteria), and Overall Survival (OS) will be reported by arm using Kaplan-Meier methods and tested using the log-rank test. The –time to castration resistance, the 2-year PSA PFS and OS proportions with 90% confidence intervals will be reported using Kaplan-Meier methods. Analyses will be completed on the ITT population.

Binomial proportions with 90% binomial confidence intervals of subjects who achieve PSA  $\leq$  0.2 ng/mL at 7 months after treatment initiation will be reported by arm. Similarly, the proportions and associated confidence intervals of subjects who achieve PSA  $\leq$  4 ng/mL at 7 months after treatment initiation will be described.

We will evaluate the distribution of pre-randomization marker levels (ALP and bone markers) among those who have and have not started ADT prior to randomization. If it appears that the prior initiation of ADT impacts the study entry bone marker levels to a fair extent, then all marker analyses will be conducted stratified by ADT initiation status. Descriptive statistics by arm will report the time to ALP progression among all subjects using Kaplan-Meier methods. ALP and serum bone markers will be reported by arm for each time-point using means or medians and corresponding measures of variability for all subjects with serum. Percentage change in ALP from baseline and changes from baseline in bone markers will be calculated for each later time point and tested between arms using a t-test or Wilcoxon rank test. If there is sufficient data, a mixed model will be used to model each endpoint over time to determine if the changes are different between treatment arms. Exploratory analysis will use separate Cox models with rPFS, PSA PFS, TTCR, and OS as the individual outcomes and treatment group, one marker, and the interaction between treatment and marker as independent covariates to find associations with outcomes. These models can be expanded to include other subject factors to determine if the marker contributes to outcome above subject factors that are known to be associated with the outcome. Similarly, logistic models can be used with 7-month PSA outcomes. The model analyses are considered exploratory for this trial. Thus, they are not powered and will not use multiple comparisons adjustments.

Worst pain will be reported from the BPI (SF) at each time point with a mean or median and the associated measure of variability and tested between arms with a t-test or Wilcoxon rank test. Comparisons at the times post-baseline will be compared between treatment arms using a paired test (t-test or Wilcoxon rank test.) WHO will be reported categorically by arm at each time point and tested between arms using the Mantel-Haenszel chi-square test. The change in WHO score from baseline will be calculated and be the outcome in a cumulative logistic model. Treatment arm will be included as an independent covariate to test if the change in pain is different between arms. Each post-baseline measure will be a separate model.

## 13 TRIAL MANAGEMENT

### 13.1 Data and Safety Monitoring Plan:

The study will be conducted in accord with University of Michigan Comprehensive Cancer Center's Data and Safety Monitoring Plan.

HCRN data and safety monitoring activities include:

- Conduct review of clinical trial for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Provide sponsor-investigator with trial progress and safety information **monthly**.
- Notification of participating sites of adverse events requiring expedited reporting
- Submit data summary reports to the DSMB for review according to DSMB Charter

### 13.2 Data Safety Monitoring Board

This study will have a Data and Safety Monitoring Board (DSMB) that will review and monitor study progress, toxicity, safety and other data from this trial. The DSMB is separate from the Data and Safety Monitoring Committee (DSMC) referred to above. The board is chaired by an independent medical oncologist external to this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician, and study team members. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet quarterly to review accrual, toxicity, response, and reporting information. Information to be provided to the DSMB may include subject accrual, treatment regimen information, adverse events, and serious adverse events reported by category, summary of any deaths on study, audit, and/or monitoring results.

The DSMB will provide a recommendation to the sponsor-investigator and HCRN after all information is reviewed. HCRN will provide this information to participating sites, who will submit it to their IRB at the time of continuing review.

### 13.3 Data Quality Oversight Activities

Remote validation of OnCore data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

There will be at least one routine visit per site per year for sites that have accrued. Additional for cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into OnCore. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Bayer or its designee as well as inspection by appropriate regulatory agencies.

### **13.4 Compliance with Trial Registration and Results Posting Requirements**

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

## **14 DATA HANDLING AND RECORD KEEPING**

### **14.1 Data Management**

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform, OnCore, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into OnCore by study site personnel from participating institutions.

### **14.2 Case Report Forms and Submission**

Generally, clinical data will be electronically captured in OnCore and correlative results will be captured in OnCore or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

### **14.3 Record Retention**

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

### **14.4 Confidentiality**

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Bayer, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

## **15 ETHICS**

### **15.1 Ethics Review**

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The site investigator must submit written approval to the HCRN office before he or she can enroll any subject into the study.

The sponsor-investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Bayer HealthCare Pharmaceuticals will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor Investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

### **15.2 Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

### **15.3 Informed Consent**

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## 16. REFERENCES

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