STUDY TITLE:

A Phase I Trial of Fractionated Docetaxel and Radium 223 in Metastatic Castration-Resistant Prostate Cancer

FUNDING SUPPORT:

Bayer HealthCare

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SYNOPSIS

TITLE	A Phase I Trial of Fractionated Docetaxel and Radium 223 (Ra-223) in Metastatic Castration-Resistant Prostate Cancer (CRPC)
PHASE	Phase I
OBJECTIVES	**Primary Objective** • Assess the safety and toxicity of a fractionated docetaxel schedule in combination with standard Ra-223 therapy in metastatic CRPC **Primary Endpoints** • Determine the maximum tolerated dose level of a fractionated 2-weekly docetaxel schedule combined with standard dosing of Ra-223 in metastatic CRPC. **Secondary Objectives** • Assess progression-free survival, time to treatment failure and overall survival. • Determine the ability of subjects to complete six cycles of the combination of docetaxel and Ra-223. • Assess PSA kinetics and objective responses (measurable disease) • Assess quality of life as measured by the Brief Pain Inventory (BPI) and Functional Assessment of Cancer Therapy – General (FACT-G) questionnaires • Assess bone biomarker outcomes (bone-specific alkaline phosphatase, urine N-telopeptides)
TREATMENTS	• Fractionated Docetaxel every 2 weeks o Planned Dose Levels: 40mg/m^2 and 50mg/m^2 o Monotherapy docetaxel for a 4 week lead-in o In combination with Ra-223, up to 6 cycles o May continue docetaxel monotherapy after completion of 6 cycles of combination at the investigator's discretion o Dose levels with prophylactic granulocyte colony stimulating factor (G-CSF) if needed • Radium-223 (55 kBq/kg) every 4 weeks for 6 cycles
INDICATION	Metastatic castration resistant prostate cancer (CRPC) with bone metastases
STUDY DESIGN	This is a Phase I study with a dose escalation cohort and an expansion cohort to determine the safety and feasibility of the combination of fractionated 2-weekly docetaxel and standard 4-weekly dose Ra-223 in metastatic CRPC. This study features a 4-week lead-in period with docetaxel monotherapy to exclude the minority of subjects intolerant of the drug in the first 4 weeks, followed by combination with Ra-223 every 4 weeks for 6 cycles in a traditional Phase I dose-escalation design. The principal anticipated overlapping toxicity of the two agents is hematologic. We hypothesize that the fractionated dosing of docetaxel will significantly mitigate the hematologic toxicity, preserve antineoplastic activity and allow for maintenance of the 4-weekly Ra-223 schedule. Docetaxel will be given at a starting dose of 40mg/m^2 every 2 weeks. After the lead-in

<table>
<tr><td></td><td>period, docetaxel will continue on Days 1 and 15, and Ra-223 will be dosed at 55 kBq/kg on Day 1 every 28 days for 6 cycles. If tolerated, we will then test docetaxel at 50mg/m^2 every 2 weeks. A provision has been made for cohorts including prophylactic granulocyte colony stimulating factor (G-CSF) after the lead-in period if neutropenia is the dose limiting toxicity at either dose level.

<table>
<tr><th>Dose Level</th><th>Docetaxel Dose (Day 1+15)</th><th>Ra-223 Dose (Day 1)</th><th>Granulocyte Colony Stimulating Factor (Day 2+16)</th></tr>
<tr><td>1</td><td>40mg/m^2</td><td>55 kBq/kg</td><td>No</td></tr>
<tr><td>1a</td><td>40mg/m^2</td><td>55 kBq/kg</td><td>Yes</td></tr>
<tr><td>2</td><td>50mg/m^2</td><td>55 kBq/kg</td><td>No</td></tr>
<tr><td>2a</td><td>50mg/m^2</td><td>55 kBq/kg</td><td>Yes</td></tr>
</table>

The maximum tolerated dose (MTD) of the combination will be defined as the highest dose-level, among those test, associated with a rate of less than a 33% dose limiting toxicity (DLT) (defined below) in the first cycle of combination therapy.

Six subjects will be accrued to each dose-level.

If the MTD is identified, we will expand with an additional 25 subjects to confirm the safety and explore preliminary anti-cancer effect. If the MTD is not identified, the study will be stopped and the expansion cohort will not be accrued.</td></tr>
<tr><td>DEFINITION OF DLT</td><td>DLT will be defined as any of the following during cycle 1 until cycle 2 day 1:
• Thrombocytopenia: platelets < 75 x 10^9/L on C1D15 or < 100 x 10^9/L on C2D1
• Neutropenia: ANC < 1000 K/mL on C1D15 or ANC < 1500 K/mL on C2D1
• Grade 3 fatigue lasting ≥ 7 days
• Other non-hematologic toxicity ≥ grade 3, lasting ≥ 48 hours at least possibly related to treatment
• Any toxicity (non-hematologic or hematologic) at least possibly related to treatment requiring dose reduction or dose interruption</td></tr>
<tr><td>ESTIMATED NUMBER OF SUBJECTS</td><td>12-18 subjects for dose escalation
An additional 25 subjects will be accrued to an expansion cohort if the MTD is identified.</td></tr>
<tr><td>PARTICIPATING CENTERS</td><td>Tufts Medical Center – Coordinating/lead center
Lahey Hospital & Medical Center</td></tr>
<tr><td>SUBJECT ELIGIBILITY CRITERIA</td><td>INCLUSION CRITERIA

1. Histologically or cytologically confirmed adenocarcinoma of the prostate
2. Documented metastatic castration resistant disease with PSA progression, radiographic progression, or both, despite medical or surgical castration
3. Two or more bone metastases detected on skeletal scintigraphy
4. No more than one prior second generation androgen receptor inhibitor
5. Eligible for docetaxel chemotherapy
6. ECOG Performance Status 0-2
7. Adequate organ function:
a. Hemoglobin > 10 g/dL
b. Absolute Neutrophil Count > 1,500 K/mL</td></tr>
</table>

	c. Platelet count > 150,000 x 10^9/L d. Total bilirubin < 1.5x upper limit of normal range, excluding Gilbert syndrome e. Serum AST < 1.5 x upper limit of normal range f. Serum ALT < 1.5 x upper limit of normal range g. Calculated creatinine clearance > 30mL/min 8. Age ≥ 18 years 9. Ongoing castration (androgen deprivation therapy or prior orchiectomy) 10. Male subjects with female sexual partners of childbearing potential must agree to use at least one highly effective methods of birth control. 11. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures. **EXCLUSION CRITERIA** 1. Prior radionuclide therapy for CRPC 2. Prior docetaxel for CRPC. (Permitted if given for castration sensitive disease > 6 months prior). 3. Antiandrogen therapy within 4 weeks of enrollment. However, patients with primary failure of secondary anti-androgen therapy OR symptomatic progression, objective progression and/or biochemical evidence of rising PSA less than 4 weeks after discontinuation of anti-androgen therapy will not have anti-androgen withdrawal responses and will not be excluded. 4. Preexisting peripheral neuropathy grade 2 or higher. 5. Other serious medical condition as judged by the investigator. 6. Active second malignancy that requires therapy. 7. Known brain or leptomeningeal metastases 8. Concurrent enrollment in any other investigational anticancer therapy 9. Treatment with any myelosuppressive agent within 30 days of enrollment 10. Presence of bulky visceral metastases, defined as any of the following: a. ≥ 4 lung lesions (at least 1cm each in size in the longest diameter) or pulmonary lymphangitic metastasis b. Liver metastases with sum of lesion diameters totaling ≥ 5cm 11. Evidence of neuroendocrine or small cell differentiation on prior biopsy 12. History of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80
STATISTICAL CONSIDERATIONS	Dose-escalation to determine the MTD as described in methods. Kaplan-Meier analysis for progression-free survival (PFS), time to treatment failure (TTTF), overall survival (OS); descriptive statistics (quantitative and qualitative) for prostate specific antigen (PSA) kinetics, objective response rate, toxicities, bone turnover biomarkers; descriptive statistics and repeated measures analysis for quality of life.
ESTIMATED ENROLLMENT PERIOD	24 months (Dose Escalation: 9 months, Expansion cohort: 15 months)
ESTIMATED STUDY DURATION	30 months

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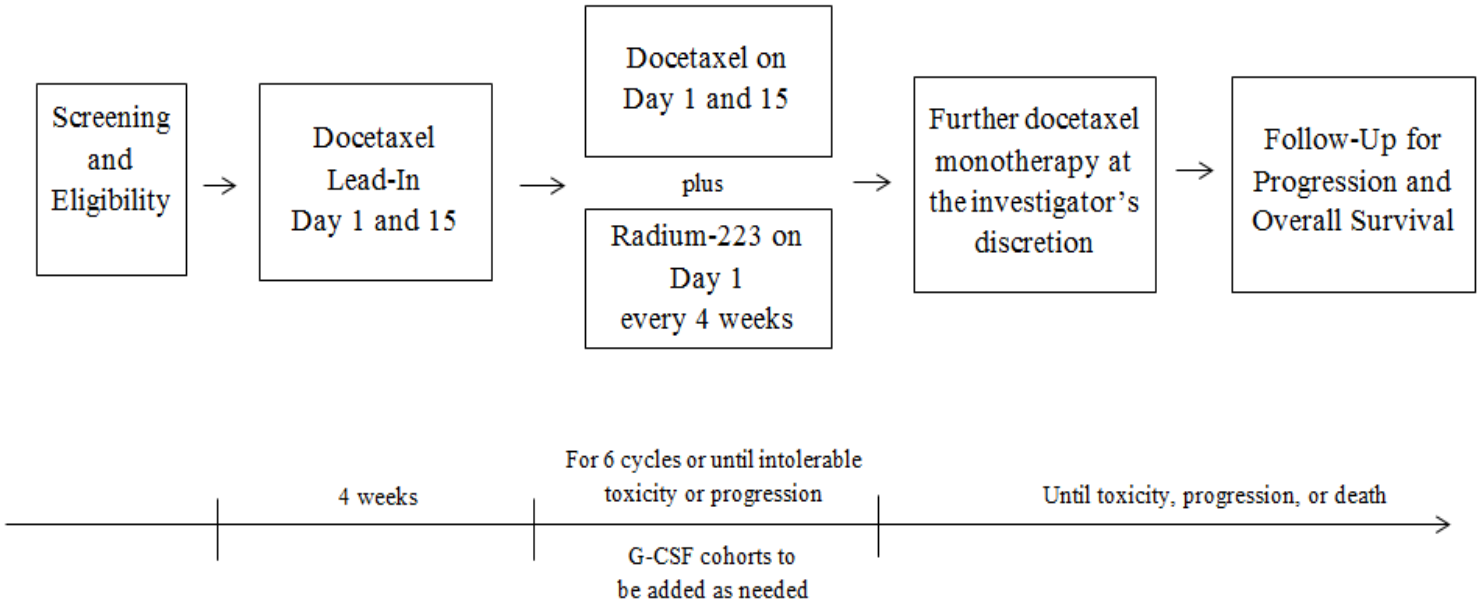
1. Study Schema



2. Introduction

2.1 Background and Rationale

Radium-223 is a novel radioisotope that improves survival and reduces symptomatic skeletal-related events in metastatic castration-resistant prostate cancer with bone metastases[1]. This therapeutic strategy exploits the highly conserved nature of the metastatic phenotype of prostate cancer characterized by progressive osteosclerotic bone metastases. In the significant majority of patients (70%), the entire visible burden of disease on radiological studies is confined to bone. In a smaller fraction of patients, lymph node and/or visceral disease coexist or emerge as the disease evolves and in these cases, bone disease may still be the dominant burden of illness.

Radium-223, however, may be best construed as a combinatorial therapy will little discernible single-agent activity in terms of objective responses in soft-tissue or visceral sites with infrequent PSA-declines >50%. In the pivotal Phase III study, Ra-223 was often combined with secondary hormonal therapy[1]. In the era of highly active anti-androgen therapies (HAAAT) including abiraterone and enzalutamide, these combinations are found to be feasible and well tolerated as expected given their non-overlapping toxicities[2]. However, a significant fraction of metastatic castration-resistant prostate cancer is characterized by aggressive biology with short periods of initial castration control and rapid PSA kinetics with symptomatic evolution or short-lived control with a HAAAT agent requiring early transition to docetaxel therapy. Crossover from one HAAAT agent to another is usually associated with poor response rates associated with the emergence of resistance mechanisms such as the AR-V7 splice variant[3]. At progression on a HAAAT agent there appears to be no loss of efficacy of docetaxel therapy[4] and in patients with bone-dominant disease refractory to potent inhibitors of the androgen axis, combinatorial therapy of docetaxel and Ra-223 is likely to enhance activity over either single agent alone.

A Phase I study of docetaxel in the standard every 3-week bolus schedule with Ra-223 was found to be limited by hematological toxicity and the need to reduce the dose of docetaxel to 60mg/m^2 every 3 weeks and to reduce the interval of administration of Ra-223 to every six weeks[5]. The impact of the reduction in dose-intensity of both regimens from those associated with improvement in overall survival remains uncertain. Several studies have indicated that fractionated schedules of docetaxel are non-myelosuppressive compared to every 3-week bolus schedules and associated with comparable clinical activity in terms of objective response rates, PSA-declines, progression-free interval, palliative responses, quality of life and overall survival [6, 7, 8].

For example, in the TAX-327 study, although overall survival benefit over mitoxantrone was not demonstrated, the PSA-progression free survival with weekly docetaxel at 30mg/m^2 appeared superior to a 3-weekly bolus schedule of docetaxel at 75mg/m^2 (M. Eisenberger, personal communication) with similar objective responses, PSA declines and improvement in quality of life in the two dosing arms. Additionally, grade 3 or 4 neutropenia was reduced from 32% (3-weekly bolus) to 2% (weekly)[6]. In the study by Oudard et al., a fractionated schedule of docetaxel showed comparable efficacy with no difference in PSA declines or time to PSA progression compared to 3-weekly docetaxel at 70mg/m^2. Fractionated dosing showed no grade 3-4 neutropenia compared to a 37% rate in the 3-weekly bolus dosing[7]. In the Finnish study, the 2-weekly regimen of docetaxel at 50mg/m^2 was compared to bolus dosing (75mg/m^2 every 3 weeks) and the fractionated dosing demonstrated longer time to treatment failure, improved overall survival and lower hematological toxicity when compared to the standard bolus dosing schedule[8]. Taken together, these data suggest that the dose-intensity of a docetaxel-Ra-223 combination may be optimized using fractionated dose-schedules of docetaxel.

Given the overall survival benefit of the 2-weekly regimen used in the Finnish study over the 3-weekly bolus dosing, this provides the rationale for the 2-weekly dose-schedule. In this study, grade 3-4 neutropenia was reduced from 53% in the 3-weekly bolus dosing to 36% in the 2-weekly group, and the rate of febrile neutropenia was reduced from 14% to 4%. G-CSF was only recommended in this study if patients had at least

one episode of febrile neutropenia. Additionally, rates of grade 3 or 4 thrombocytopenia and anemia in the 2-weekly group were each just 1%.

Although the rates of grade 3 and 4 neutropenia in the phase III Ra-223 study were only 2%, there may be an incremental effect in the combinatorial regimen. We thus propose starting at a dose level of 40mg/m^2 prior to dose escalation to the dose-level of 50mg/m^2 used in the Finnish study, with the provision to use G-CSF at either dose-level as needed for dose-limiting neutropenia. If required, the study will employ next-day dosing of G-CSF. According to the new drug application submitted for Ra-223 in December, 2012, the use of growth factor with Ra-223 was noted in 1.5% of the 600 patients treated in the experimental (Ra-223) arm of the ALSYMPCA (BC1-06) trial[1]. Additionally, subjects in the ongoing trial combining Ra-223 and docetaxel at different dose intensities[5] have only required growth factor "occasionally" (personal correspondence with PI, Dr. Michael Morris). Neither of these trials specified a timing interval for the growth factor other than the conventional plan and there have been no signs of excess toxicity in either group with the use of growth factor.

Additionally, given that Ra-223 specifically targets bone metastases, we will exclude patients with evidence of bulky visceral (lung and liver) metastases (defined in Section 4.2), and we will exclude tumors of neuroendocrine or small cell differentiation, for which docetaxel does not represent optimal systemic therapy.

Hypothesis: We hypothesize that a fractionated dose-schedule of 2-weekly docetaxel in combination with standard Ra-223 55 kBq/kg every 4 weeks will be feasible and will define a novel combination for future study in CRPC with bone metastases. Over the long term, an optimized dose-schedule of fractionated docetaxel and Ra-223 may prove to be a superior approach compared to bolus docetaxel or Ra-223 alone or in sequence in CRPC with bone metastases in terms of disease control and overall survival.

2.2 Risks to Subjects

The side effects of docetaxel or Ra-233 alone are discussed in Section 10.

The principal anticipated toxicities of the combination will be myelosuppression, with the potential complication of febrile neutropenia, and fatigue. Other drug-interactions that generate a side-effect profile distinct from either docetaxel or Ra-223 alone are not anticipated. The fractionated dosing schedule should mitigate the hematologic risk and subjects who participate should not be placed at undue risk.

2.3 Potential Benefits to Subjects

Single-agent docetaxel and radium-223 have both been associated with an improvement in overall survival in this population of patients[1,6].

2.4 Alternatives

Subjects could receive single agent docetaxel or Ra-223, or alternative agents (e.g. Sipuleucel-T[9], abiraterone[10], enzalutamide[11]), at the discretion of their treating physician.

3 Objectives

3.1 Primary Objective

- Assess the safety and toxicity of docetaxel and Ra-223 combination therapy in CRPC

3.2 Primary Endpoint

- The primary endpoint is the maximum tolerated dose of fractionated 2-weekly docetaxel combined with standard dosing of Ra-223

3.3 Secondary Objectives

- Describe qualitative and quantitative toxicities
- Assess progression-free survival, time to treatment failure, and overall survival.
- Determine the ability of subjects to complete six cycles of planned combination of docetaxel and Ra-223.
- Assess PSA kinetics and objective responses (measurable disease)
- Assess quality of life via the BPI and the FACT-G questionnaire
- Assess bone marker outcomes: bone-specific alkaline phosphatase and urine N-telopeptides

4 Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed (at local institution), adenocarcinoma of the prostate
2. Documented metastatic castration resistant disease with PSA progression, radiographic progression, or both, despite receiving LHRH analogue therapy or orchiectomy with a serum testosterone level of 50ng/dL or less.
    a. PSA progression is defined as three successive rising PSA values with an interval of at least one week between determinations
    b. Radiographic progression is defined by either RECIST 1.1 criteria or at least two new lesions on bone scan
3. Two or more bone metastases detected on skeletal scintigraphy
4. No more than one prior second generation androgen receptor inhibitor (e.g. enzalautamide, abiraterone, or other experimental second generation androgen inhibitor)
5. Eligible for docetaxel chemotherapy
6. ECOG Performance Status 0-2
7. Adequate organ function:
    a. Hemoglobin > 10 g/dL
    b. Absolute Neutrophil Count > 1,500 K/mL
    c. Platelet count > 150,000 x 10^9/L
    d. Total bilirubin < 1.5x upper limit of normal range, unless subject has Gilbert's Disease
    e. Serum AST < 1.5 x upper limit of normal range
    f. Serum ALT < 1.5 x upper limit of normal range
    g. Creatinine Clearance (estimated by Cockgroft-Gault Formula) > 30mL/min
8. Age ≥ 18 years
9. Surgical castration with bilateral orchiectomy or maintenance of chemical castration (testosterone ≤ 50ng/dL) (e.g. with Gonadotropin Releasing Hormone (GnRH) analogue)
10. Male subjects with female sexual partners of childbearing potential must agree to use at least one highly effective methods of birth control, such as condoms, birth control pills, IUDs, or abstinence.
11. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures.

4.2 Exclusion Criteria

1. Prior radionuclide therapy for CRPC
2. Prior docetaxel for CRPC. Prior docetaxel is permitted if given previously in the setting of castration sensitive disease, but not within previous 6 months of enrollment.
3. Antiandrogen therapy within 4 weeks of enrollment. However, patients with primary failure of secondary anti-androgen therapy OR symptomatic progression, objective progression and/or biochemical evidence of rising PSA less than 4 weeks after discontinuation of anti-androgen therapy will not have anti-androgen withdrawal responses and will not be excluded.
4. Preexisting peripheral neuropathy grade 2 or higher.

5. Other serious medical condition as judged by the investigator.
6. Active second malignancy that requires therapy.
7. Known brain or leptomeningeal metastases.
8. Concurrent treatment with an investigational antineoplastic agent in a clinical trial.
9. Treatment with any myelosuppressive agent within 30 days of enrollment.
10. Presence of bulky visceral metastases (measured locally), defined as any of the following:
    a. ≥ 4 lung lesions (at least 1cm each in size in the longest diameter) or pulmonary lymphangitic metastasis
    b. Liver metastases, with sum of diameters totaling ≥ 5cm
11. Evidence of neuroendocrine or small cell differentiation on prior biopsy
12. History of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80

4.3 Withdrawal of Subjects

A subject may be withdrawn by the sponsor-investigator if enrollment into the trial is inappropriate or for administrative and/or other safety reasons.

Specific details regarding discontinuation or withdrawal are provided below. The subject should be offered alternative standard of care treatment if withdrawn from the study.

A subject must be discontinued from the trial treatment for any of the following reasons:

- Confirmed disease progression by criteria as outlined in Section 6
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Site investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- Subject refuses further treatment
- Administrative reasons
- The subject withdraws consent.
- The subject is lost to follow-up

Subjects who begin the lead-in phase but are unable to proceed to Cycle 1 Day 1 of the combination treatment will be withdrawn. The reason for withdrawal must be documented. Data collected will include demographics, baseline disease information, and any assessment done during the docetaxel lead-in phase.

4.4 Recruitment and Registration

4.4.1 Recruitment Methods

Subjects will be recruited by providers at the Tufts Medical Center Cancer Center and participating sites. The trial details will be posted to the Tufts Medical Center Clinical Trials website. Local IRB's must approve all advertising used to recruit subjects for the study prior to implementation.

4.4.2 Payment

Subjects will not receive money, gifts, or any other payment for participating in this study.

4.4.3 Reimbursement

Subjects will not be reimbursed for their expenses, such as travel, parking, meals, or any other study related costs.

4.4.4 Subject Registration

A subject number will be assigned for each subject who has signed an informed consent form (ICF). If a subject has completed all screening requirements and meets all of the eligibility criteria, a Subject Registration Form will be submitted to Tufts Medical Center for eligibility review and approval. If approved, registration will be implemented via the Internet connection.

5 Study Design

5.1 Study Timelines

- A subject will be on lead-in treatment with docetaxel for 4 weeks, active combinatorial treatment for 6 cycles (4-week cycles), or until disease progression, withdrawal of consent or unacceptable toxicity, and then seen in follow up every 12 weeks until disease progression. After progression, they will be followed every three months for overall survival.
- All subjects in the dose escalation cohort (12-18) and the expansion cohort (25) should be enrolled within approximately 24 months; 9 months in dose escalation cohort and 15 months in the expansion cohort.
- Primary analysis will be accomplished 3 months after the final patient has completed cycle 1.

5.2 Procedures

5.2.1 Lead-In

A 28-day lead-in period will occur in both the dose escalation and expansion cohorts of the trial. In this lead-in period, all subjects will receive docetaxel at the currently enrolling Dose Level on day 1 and day 15 (+/- 3 days) *without* Ra-223. If the subject is able to tolerate docetaxel without troublesome grade 2 or any grade 3-4 toxicity, cycle 1 of combined docetaxel and Ra-223 will commence. Subjects who drop out or require dose-reductions of docetaxel for toxicity during lead-in will be replaced and will not proceed to combination therapy. No planned growth factor will be given for any dose level during the lead-in phase and any subjects experiencing grade 3-4 neutropenia during the lead-in phase would be replaced. It is anticipated that less than 10% of patients registered to the protocol will experience lead-in toxicity.

5.2.2 Dose Limiting Toxicities

DLT will be principally defined by the ability to receive all planned doses of docetaxel and Ra-223 in cycle 1 and the ability to receive both agents on time on cycle 2 day 1.

DLT will be defined as any of the following during cycle 1 until cycle 2 day 1:
- Thrombocytopenia: platelets $< 75 \times 10^9$/L on C1D15 or $< 100 \times 10^9$/L on C2D1
- Neutropenia: ANC < 1000 K/mL on C1D15 or ANC < 1500 K/mL on C2D1
- Grade 3 fatigue lasting ≥ 7 days
- Other non-hematologic toxicity ≥ grade 3, lasting ≥ 48 hours at least possibly related to treatment

- Any toxicity (non-hematologic or hematologic) at least possibly related to treatment requiring dose reduction or dose interruption

5.2.3 Treatment Schedules

Subjects who are able to tolerate the 28-day lead-in with docetaxel will progress to cycle 1 of combined therapy. Each cycle will consist of 28 days.

Fractionated docetaxel every 2 weeks will be studied at two dose-levels in combination with standard dosing of Ra-223 (55 kBq/kg every 4 weeks). Docetaxel will be given on days 1 and 15 (+/- 3 days) of each 28-day cycle. If cohorts with pegfilgrastim (G-CSF) support are needed for a DLT of neutropenia, a cohort of subjects would receive G-CSF 6mg subcutaneously on days 2 and 16, on the day after all doses of docetaxel (except for the lead-in period as in Section 5.2.1). Ra-223 will be given on day 1 of each cycle (+/- 5 days).

Six subjects will be enrolled at each dose level. Up to six subjects will be enrolled at a time per dose level. Enrollment for the next dose level will not proceed until at least five subjects from the previous dose level have completed cycle 1 of combined therapy without dose-limiting toxicity (DLT).

5.2.4 Dose Escalation and Granulocyte Colony Stimulating Factor

Table 1. Dose Level Schedule

Dose Level	Docetaxel Dose (Day 1+15)	Ra-223 Dose (Day 1)	Granulocyte Colony Stimulating Factor (6mg on Day 2+16)
1	40mg/m^2	55 kBq/kg	No
1a	40mg/m^2	55 kBq/kg	Yes
2	50mg/m^2	55 kBq/kg	No
2a	50mg/m^2	55 kBq/kg	Yes

- At Dose Level 1, we will enroll six subjects: If 0-1 subjects experience a DLT, we will open enrollment to Dose Level 2
- If ≥ 2 subjects experience a DLT due to neutropenia, we will open enrollment to Dose Level 1a
- If ≥ 2 subjects experience a non-neutropenia DLT, we will stop enrollment.

If Dose Level 1a is needed, we will enroll six subjects:

- If 0-1 subjects experience DLT, we will open enrollment to Dose Level 2a
- If ≥ 2 subjects experience a DLT due to neutropenia, we will stop enrollment.
- If the rate of non-neutropenia DLT is < 33% for combined Dose Level 1 and 1a, we will open enrollment to Dose Level 2a. If this this rate is ≥ 33%, we will stop enrollment.

If Dose Level 2 is needed, we will enroll six subjects:

- If 0-1 subjects experience DLT, we will open an expansion cohort at Dose Level 2
- If ≥ 2 subjects experience DLT due to neutropenia, we will open enrollment to Dose Level 2a.
- If ≥ 2 subjects experience a non-neutropenia DLT, we will open an expansion cohort at Dose Level 1

If Dose Level 2a is needed, we will enroll six subjects:

- If 0-1 subjects experience DLT, we will open an expansion cohort at Dose Level 2a
- If ≥ 2 subjects experience a DLT due to neutropenia, we will open an expansion cohort at Dose Level 1a

- If the rate of non-neutropenia DLT is < 33% for combined Dose Level 2a and Dose Level 2 (if previously opened), we will open an expansion cohort at Dose Level 2a. If this this rate is ≥ 33%, we will open an expansion cohort at Dose Level 1a

Once a maximum tolerated dose (MTD) of docetaxel has been reached, the investigators will consider the MTD and any toxicity seen in subsequent cycles, and select a recommended dose level for the expansion cohort with an additional 25 subjects. If the MTD is not identified, the study will be stopped and the expansion cohort will not be accrued.

5.2.5 Pre-Medications

For docetaxel administration, the recommended pre-medication regimen is dexamethasone 8mg at 12 hours, 3 hours and 1 hour before the docetaxel infusion. The preferred route is intravenous, but oral is also acceptable. Other schedules are also acceptable if local practice is different.

5.2.6 Concurrent Therapy

- Prednisone 5mg twice daily will be co-administered. This can be dose-reduced or eliminated at the discretion of the investigator for side effects, as it has no known therapeutic value.
- While on-study, subjects who have not undergone orchiectomy should maintain testosterone at castrate levels (< 50ng/dL) using GnRH agonist/antagonist therapy.
- Bone health agents such as bisphosphonates or denosumab should be used according to NCCN guidelines, unless contraindicated, for prevention of skeletal-related events. Subjects may take calcium and vitamin D supplements.
- Granulocyte colony stimulating factor support (pegfilgrastim) can be used either as prophylaxis starting C1D1 as described in section 5.2.4 or as needed for dose limiting neutropenia that occurs after C2D1 as described in Section 5.2.7.

5.2.7 Dose Modification and Toxicity Management

A provision will be made for any toxicities incurred after cycle 2, day 1 that require delay and dose adjustment. By definition, these would not qualify as a DLT.

For any adverse event after C2 D1 that would otherwise meet criteria for DLT (defined in Section 5.2.2), treatment should be withheld until toxicity resolves (no longer meeting these criteria) and resumed at a lower dose as per Table 2 (below). Of note, if neutropenia or neutropenic fever limits further dosing after C2 D1, G-CSF 6mg on Day 2 and Day 16 may be added at the investigator's discretion once the neutropenia resolves.

Table 2. Dose Reductions after Cycle 2, Day 1

Treating Dose of Docetaxel	Dose-reduction for toxicity
50mg/m^2	40mg/m^2
40mg/m^2	30mg/m^2
30mg/m^2	Subject must come off study for recurrent toxicity

5.2.8 Contraception

Male subjects with female sexual partners of childbearing potential must agree to use at least one highly effective methods of birth control, such as condoms, birth control pills, IUDs, or abstinence.

5.2.9 Treatment Discontinuation

Combination docetaxel and Ra-223 treatment will be discontinued for withdrawal of consent, after 6 cycles of therapy, or for progressive disease, unacceptable toxic effects, or death. Subjects may also be withdrawn from the trial at the discretion of the site investigator as outlined by Section 4.3. Patients may continue on docetaxel therapy alone after completion of 6 cycles of combination therapy, in the absence of disease progression or limiting toxicity, at a dose-schedule at the discretion of the treating physician.

5.3 Evaluations

Refer to the "Study Schedule of Events" in the Appendix for the study calendar.

5.3.1 Screening

Within 28 days prior to registration for protocol therapy:

- Signed informed consent
- Demographic Data (date of birth, age, racial group)
- Diagnosis confirmation via pathology report from original or most current biopsy.
- CT scan of the chest, abdomen, and pelvis
- Radionuclide bone scan

Within 14 days prior to registration for protocol therapy:

- Medical history and physical exam
- Vital signs including blood pressure, heart rate, temperature, height (screening), weight and ECOG performance status
- Review inclusion and exclusion criteria to ensure eligibility
- Record adverse events and concomitant medications
- Laboratory studies including
    - Complete blood count (CBC) with differential and platelet
    - Complete Metabolic Profile (CMP) including: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphate, alkaline phosphatase, aspartate aminotransferase (also known as SGOT or AST), alanine aminotransferase (also known as SGPT or ALT), total bilirubin, total protein, and albumin.
    - PSA
    - Testosterone
- Correlative Studies
    - Bone-specific Alkaline Phosphatase
    - Urine N-telopeptide
- Surveys:
    - FACT-G
    - BPI

5.3.2 On Treatment

5.3.2.1 Docetaxel Lead-in Period:

- Physical exam, vital signs, weight, ECOG performance status, concomitant medication review, adverse event assessment on day 1 and day 15
- CBC and CMP will be checked on day 15 prior to docetaxel administration.

5.3.2.2 Cycle 1 Day 1 of Combination Therapy

- Physical exam
- Vital signs, weight and ECOG performance status
- Concomitant medication review
- Toxicity and adverse event assessment; evaluate for continuation to combination therapy

- Laboratory studies including
  - CBC with differential and platelet
  - CMP
  - PSA
- Correlative Studies
  - Bone-specific Alkaline Phosphatase
  - Urine N-telopeptide
- Surveys
  - FACT-G
  - BPI

5.3.2.3 Cycle 1 Day 15 of Combination Therapy (and all subsequent Day 15's through cycle 6)

- Physical exam
- Vital signs, weight and ECOG performance status
- Concomitant medication review
- Toxicity and adverse event assessment
- Laboratory studies including
  - CBC with differential and platelet
  - CMP

5.3.2.4 Day 1 of All Further Cycles (Cycles 2-6)

- Physical exam
- Vital signs, weight and ECOG performance status
- Concomitant medication review
- Toxicity and adverse event assessment; review for DLTs
- Laboratory studies including
  - CBC with differential and platelet
  - CMP
  - PSA

5.3.2.5 Cycle 3 Day 1 (in addition to Section 5.3.2.4)

- Testosterone (every 12 weeks)
- Correlative Studies
  - Bone-specific Alkaline Phosphatase
  - Urine N-telopeptide
- Surveys
  - FACT-G
  - BPI
- Imaging
  - CT scan of the chest, abdomen, and pelvis (+/- 7 days)
  - Radionuclide bone scan (+/- 7 days)

5.3.2.6 Cycle 5 Day 1 (in addition to Section 5.3.2.4)

- Correlative Studies
  - Bone-specific Alkaline Phosphatase
  - Urine N-telopeptide
- Surveys
  - FACT-G
  - BPI

5.3.2.7 Cycle 6 Day 1 (in addition to Section 5.3.2.4)

- Testosterone (every 12 weeks)

- Imaging
    - CT scan of the chest, abdomen, and pelvis (+/- 7 days)
    - Radionuclide bone scan (+/- 7 days)

5.3.3 Restaging Evaluations

CT scan of the chest, abdomen, and pelvis and radionuclide bone scan will be done at Screening, Cycle 3 Day 1 (+/- 7 days), Cycle 6 Day 1 (+/- 7 days), and every 12 weeks thereafter (+/- 7 days) until disease progression. They can also be done at any time at the discretion of the site investigator to assess for suspected progression.

5.3.4 End of Treatment (EOT) Visit

All subjects who have completed 6 cycles of planned therapy and those who terminate the study treatment before completion of 6 cycles will require an end of treatment visit. This should occur four weeks (+/- 7 days) after last Ra223 dose and prior to their next systemic therapy.

The following are required at the end of treatment visit:

- Physical exam
- Vital signs, weight and ECOG performance status
- Concomitant medication review
- Toxicity and adverse event assessment; review for DLTs
- Laboratory studies including
    - CBC with differential and platelet
    - CMP
    - PSA
    - Testosterone (if not collected within the last 12 weeks)
- Correlative Studies
    - Bone-specific Alkaline Phosphatase
    - Urine N-telopeptide
- Surveys
    - FACT-G
    - BPI

5.3.5 Follow up

Subjects with AE's incurred during treatment that have not resolved by the EOT Visit should continue to be seen every 2-4 weeks until AE's resolve or until they begin a new line of systemic therapy.

Subjects who have completed six cycles of combinatorial treatment or discontinued treatment for any reason without documented disease progression will be followed every 12 weeks with physical exam, concomitant medication review, laboratory studies (CBC with differential and platelet, CMP, PSA, and testosterone), CT scan of the chest, abdomen, and pelvis and radionuclide bone scan until documented disease progression. Additionally, every 12 weeks, they will complete the FACT-G and BPI surveys until disease progression or start of a new therapy.

Once disease progression is documented, subjects will enter a survival follow up period every 3 months until death. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

6 Criteria for Disease Evaluation

6.1 Definition of Progressive Disease

Isolated increase of PSA in the absence of symptoms or evidence of radiographic progression is not considered disease progression. The definition of progressive disease for the study will be as follows, modified from the Prostate Cancer Working Group 2 (PCWG2)[12] Criteria:

- Two or more new bone lesions on radionuclide bone scan. If this occurs at the first post-treatment scan, progression should be confirmed by a second scan done at least six weeks later showing at least two new additional bone lesions not previously identified.
- **OR** RECIST version 1.1 criteria
- **OR** increase of PSA by 25% or more from the nadir or baseline with at least one new bone lesion on radionuclide bone scan. Patients with this composite measure of disease progression, without symptomatic or objective measures of disease progression as defined in this section, may continue on protocol-based therapy until disease progression is further confirmed with additional rise in the PSA (≥1ng/ml) in ≥ 4 weeks from this time and/or one additional bone lesion by bone scan performed at least six weeks later.
- **OR** increasing pain strongly attributable to metastatic prostate cancer (*e.g.* malignant bony pain at a known metastatic site). Pain progression is defined as an increase of two or more points from baseline in the worst pain in the last week on the BPI questionnaire, observed at two consecutive evaluations ≥ 4 weeks apart OR the initiation of short or long acting opioid use for pain.
- In cases of progressive disease based on symptoms, corroboration with appropriate radiologic studies is recommended. If progression is defined by bone scan alone, then time of progression is defined at the time of the appearance of the first new bone lesion.
- External beam radiation therapy delivered to a single site of disease for symptom control will not qualify, on its own, as progressive disease. A criterion above must still be met.

6.2 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

6.2.1 Measurable disease

The presence of at least one measurable lesion (by local institution measurement). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if the investigator is uncertain if the lesion is neoplastic.

6.2.2 Measurable lesions

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

6.2.3 Non-measurable lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm 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 as non-measurable.

Note: 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.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

6.2.4 Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

6.2.5 Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor

6.2.6 Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3 Response Criteria

6.3.1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

6.3.2 Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or 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. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor-investigator.

6.4 Evaluation of best overall response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ not evaluated	No	PR
SD	Non-CR/ Non-PD/ not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

6.5 Definitions for Response Evaluation – RECIST version 1.1

6.5.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

6.5.2 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.

6.5.3 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 for progressive disease the smallest measurements recorded since treatment started).

6.5.4 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.

6.5.5 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

6.5.6 Time to Progression
A measurement from the date of enrollment until the first event, which meets criteria for disease progression. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

6.5.7 Progression Free Survival

A measurement from the date of enrollment until the criteria for disease progression are met or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation or the study ending date.

6.5.8 Time to Treatment Failure

A measurement from the date of enrollment until the first event which meets criteria for treatment failure. Treatment failure is defined as progression, unacceptable toxic effects, death, or discontinuation of combination treatment for any other reason. Subjects who have not reached treatment failure will be right-censored at the date of the last disease evaluation or the study ending date.

6.5.9 Overall Survival

Overall survival is defined by the date of enrollment to date of death from any cause. Subjects who are still alive will be right-censored at the date of the last disease evaluation or the study ending date.

7 Ethics and Protection of Human Subjects

7.1 Ethics Review

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

The site 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.

Modifications to the study protocol will not be implemented by the principle investigator at Tufts Medical Center without discussion and agreement by Bayer. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment will be submitted to the IRB. Any deviations from the protocol must be explained and documented by the investigator.

7.2 Ethical Conduct of the Study

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

7.3 Informed Consent Process

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 will 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 (ICF). A copy of the signed Written Informed Consent Form must be given to the subject.

It is anticipated that non-English speakers will be enrolled in this research study. At Tufts Medical Center, the Short Form is allowed to consent these patients. The short-form consent procedure will be followed according to IRB policy. The PI or Co-Is will employ a translator to assist in conducting the consent interview. Translated short form documents will be provided in the appropriate language.
The additional sites will have to ensure that they are also following their local IRB policy for consenting non-English speaking patients.

7.4 Confidentiality

The Investigator must ensure that each subject's privacy is maintained as described below. On the eCRFs or other documents submitted to the Sponsor or its designee, subjects must be identified by no more than their date of birth or age, sex, and study-specific site and subject numbers. Documents that are not for submission to the Sponsor (e.g. signed ICFs) should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor, of regulatory agencies, and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that the above named representatives may review study-related records from subjects.

7.5 Publication policy

Bayer recognizes the right of the investigator to publish results upon completion of the study. All Investigator Initiated studies are the property of the investigator and publications generated from such studies are at the discretion of the investigator. Bayer strongly encourages investigators to publish the results of all studies supported through the Investigator Initiated Research (IIR) Program.

As an important milestone to the IIR, Bayer encourages all investigators to submit a draft manuscript of the supporting publication(s) or abstract to submission for a courtesy review prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and will not be withheld unreasonably. All relevant aspects regarding data reporting and publication will be part of the contract between Bayer and the investigator/institution. Therefore, Tufts Medical Center will only be sharing de-identified data with Bayer, the funder of this study.

The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

7.6 Research Related Injury

If subjects are injured or hurt as a result of taking part in this study and need medical treatment, they should contact the study doctor.

Emergency medical treatment should be provided to subjects if they are hurt or get sick as a direct result of being in this research study. Any needed medical care should be available at the usual cost. All needed facilities, emergency treatment, and professional services should be available to subjects participating in this study.

8 Adverse Event Monitoring

8.1 Definitions

8.1.1 Adverse Event

Adverse event (AE) means any untoward medical occurrence in a study subject administered an investigational drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with participation in an investigational study, whether or not considered related to the investigational product. An AE is any sign, symptom, or diagnosis that appears or changes in intensity during the course of the study. An AE may be an intercurrent illness or injury that impairs the well-being of the subject.

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Investigators should refer to the Safety Information section of the current IB for Ra 223 dichloride, including the DCSI (development core safety information), for the expected side effects of Ra 223 dichloride. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

8.1.2 Serious Adverse Event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.
b. Is life-threatening.
   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
c. 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 12 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.
d. Results in persistent or significant disability / incapacity.
   Disability means a substantial disruption of a person's ability to conduct normal life's functions.
e. Is a congenital anomaly / birth defect.
f. Is another medically important serious event as judged by the investigator.

8.2 Adverse Event Reporting

8.2.1 Site Requirements for Recording Adverse Events

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to the study drug. Each

AE will be assessed by the site investigator with regard to the following categories:

- Seriousness
- Intensity
- Causal relationships to study drug (to be assessed separately for concomitant agents)
- Study treatment action
- Other specific treatment of AE
- Outcome

Seriousness should be assessed in accordance with the International Conference on Harmonisation's Technical Requirements for Clinical Safety Data Management (E2A Guidelines).

Intensity should be assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v4).

Causal relationship between an AE and the administration of treatment is a clinical decision based on all available information. The causality assessment should be done separately for each study treatment. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.
or
2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Action taken with study treatment. Any action on study treatment to resolve the AE is to be documented using the categories listed below. The study treatment action should be recorded separately for each study treatment.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Dose increased
- Not applicable

- Unknown

Other specific treatment(s) of adverse events
- None
- Remedial drug therapy
- Other

The outcome of the AE is to be documented as follows:
- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

AEs that occur before the first study drug administration, concomitant illnesses, which existed before study entry, but did not worsen during the treatment period and any pre-existing conditions are known as "pre-treatment AEs" and by definition are "unrelated" to study drug. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, electrocardiograms [ECG], reported by subject), must be recorded in the subject's medical record.

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the site investigator, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

All bone fractures need to be reported as either AE(s) or SAEs if the criteria of SAE are met, regardless of the investigator's causality assessment, preferentially up to 3 years, but for a minimum of 1 year after the last dose of radium-223.

8.2.2 Site Requirements for Reporting Serious Adverse Events (SAEs)

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the IRB and Regulatory Authorities.

Sites must report SAEs that occur from the time of informed consent to 30 days following last dose of study drug. SAEs should be reported to Tufts Medical Center within 24 hours of discovery of the event regardless of relation to the study drug, who will in turn report these directly to Bayer. Reports must include the following minimum information:

- The name and contact information of the reporter
- The name of the study drugs
- A description of the reported SAE
- A patient identified by one or more of the following:
    - Patient initials
    - Patient number

- Knowledge that a patient who experienced the adverse event exists
- Age
- Sex

- An investigator assessment of study drug causality 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

Serious adverse events occurring after this 30-day period and coming to the attention of the site investigator must be reported only if they are considered (in the opinion of the site investigator) causally related to the investigational drug.

The Investigator must report serious adverse drug reactions (SADRs) using either:

- An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html

OR

- A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

- Electronic Mailbox: DrugSafety.GPV.US@bayer.com
- Facsimile: (973) 709-2185
- Address (Mail Only): Global Pharmacovigilance - USA
Bayer HealthCare
P.O. Box 915 Whippany, NJ 07981-0915
- Address (FDX): 100 Bayer Blvd., Whippany, NJ 07981
- Address (UPS): 67 Whippany Road, Whippany, NJ 07981
- Phone: 1-888-842-2937

8.2.3 Pregnancy Reporting

Pregnancies occurring in a female partner of a male subject and pregnancy outcomes must be reported by sites to Tufts Medical Center **within 24 hours** of discovery of event. Any pregnancies will be followed until to term or until termination of the pregnancy via monthly interviews with the subject or his partner. The outcome of the pregnancy (delivery, neonate status including presence or absence of congenital anomalies or pregnancy termination, as applicable) will be reported to Tufts Medical Center.

9 Statistical Methods

9.1 Definition of Primary Endpoint

The primary objective is to assess safety and toxicity. The primary endpoint is the MTD of the combination of fractionated docetaxel and Ra-223. This is defined as the maximum Dose Level explored in which the DLT rate is less than 33% at the beginning of cycle 2.

9.2 Definitions of Secondary Objectives

Progression-Free Survival, Time to Treatment Failure, Objective Response Rate and Overall survival
These are defined in Section 6.

Ability to complete six cycles of combination therapy
This is defined as receiving both lead-in doses of docetaxel and all 6 cycles of combination docetaxel and Ra223 on time (+/- 7 days).

PSA Kinetics
PSA values will be recorded at Screening, on Day 1 of each cycle of therapy, at the EOT visit, and in follow up every 12 weeks until progressive disease occurs.

Quality of Life
This will be measured using FACT-G and BPI questionnaires. These will be administered at Screening, C1D1, C3D1, C5D1, EOT visit, and in follow up every 12 weeks until progressive disease occurs or the subject initiates a new systemic therapy.

Bone Marker Outcomes
Bone-Specific Alkaline Phosphatase and Urine N-telopeptide will be recorded at Screening, C1D1, C3D1, C5D1 and at EOT visit.

9.3 Statistical Analysis

9.3.1 Analysis Plan for Primary Objectives/Aims

Maximum Tolerated Dose
In the dose escalation cohort, the MTD will be determined at the time the last subject in the study is due to begin cycle 2 of combination treatment. It will be determined by the highest dose level explored associated with less than a 33% DLT rate in the first cycle of combination therapy.

9.3.2 Analysis Plan for Secondary Objectives/Aims

The goal of the secondary objectives is primarily descriptive. This information can be used in future trials to inform about expected effect size and sample size.

Progression Free Survival
Subjects from the dose escalation and expansion cohorts whose disease has not progressed by EOT visit will be followed every 12 weeks. PFS will then be calculated as a time-to-event endpoint and estimated with the Kaplan Meier method and swimmer plot. The historical median progression-free survival following docetaxel based therapy for metastatic castration-resistant prostate cancer is approximately 6 months.[13,14] With a sample size of 37-43 evaluable subjects, the dose escalation and expansion cohorts will have a 73-79% power to detect a 50% increase in median PFS from 6 to 9 months, at the significance level of 0.05, with a one-sided test. The time to completion of accrual (dose escalation and expansion cohorts) is projected at 24 months with a follow-up time of 12 months following last participant entry.

Time to Treatment Failure (TTTF)
Once Treatment Failure is met (defined in Section 6), TTTF will be calculated as a continuous variable, described with a swimmer plot and estimated with the Kaplan Meier method.

Overall Survival

Once disease progression is documented, subjects will enter a survival follow up period every 3 months until death. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Overall survival will be annotated as a continuous variable after death occurs and estimated using the Kaplan Meier method.

Objective Responses
This is described in Section 6. These will be annotated as a continuous variable and described as proportions.

Ability to complete 6 cycles of combination therapy
After the last treatment on study, the number of subjects who were able to receive all doses of docetaxel and Ra-223 on time will be annotated as a proportion.

Continuously Measured Secondary Outcomes (PSA, Quality of Life, Bone Marker Outcomes)
For the continuously measured secondary outcomes (PSA, Quality of Life and Bone Marker Outcomes), we will calculate the descriptive statistics (means and standard deviations) at each time point (number of days) when the outcome data are collected. These will use continuous variables (PSA value, BPI and FACT-G questionnaire results for Quality of Life and bone-specific alkaline phosphatase and urine N-telopeptides for bone markers). Since these outcomes are repeatedly measured over time on a subject, we will also use mixed effect models to explore the temporal trajectories for the outcome changes over time in response to the treatment. The mixed effect models will be used for non-hypothesis driven purpose, i.e. no statistical comparisons will be made from these models. Rather, these models will allow us to explore the outcome change over time by accounting for the random intercepts and slopes among projected trajectory lines for all individuals. The overall projected trajectory lines can then be plotted for visual inspections and can serve as the foundation of generating the hypothesis for the future studies.

PSA kinetics will additionally be annotated as waterfall plots. We will also calculate PSA Response Rate of > 50% and > 90% as a categorical variable and these will be described as proportions. And bone-specific alkaline phosphatase and urine N-telopeptides changes will be also annotated with waterfall plots.

9.4 Number of Subjects

Planned number of subjects across two sites: Dose escalation: 12-18, Expansion cohort: 25

9.5 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 complete the docetaxel lead-in and receive at least one dose of combination docetaxel AND Ra-223.

9.6 Replacement Rules

Subjects intolerant of docetaxel in the lead-in period will be removed from the trial and replaced from the study.

9.7 Study Duration

The treatment phase will continue until a subject has completed 6 cycles of planned therapy or terminates the study treatment before completion of 6 cycles. The follow up phase will continue until all subjects have progressive of disease, initiate a non-study treatment, withdraw consent, or are lost to follow-up. Long-term follow up for overall survival will continue every 3 months until death occurs or subjects are lost to follow up.

10 Drugs

10.1 Radium (Ra-223) dichloride

The investigational product, Radium-223 dichloride (223RaCl2) is a selective targeted high linear energy transfer radiation emitting alpha particle that is a sterile ready-to-use aqueous solution for intravenous injection. The active moiety is the alpha particle emitting nuclide Ra-223, present as a divalent cation (223Ra2+), which forms a complex with hydroxyapatite in areas of increased bone turnover. Energy released from the active moiety causes potent cytotoxicity by inducing double stranded DNA breaks. Half-life (t1/2)of 11.4 days. It is a sterile clear, colorless, isotonic, solution to be administered intravenously.

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

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

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

10.1.1.1 Dose

Doses are given as kilobecquerel (kBq) per kilogram body weight, with the corresponding dose given in millicurie (mCi) per kilogram in parenthesis. The term "dose" is used to describe the quantity of radioactivity from Radium Ra 223 dichloride administered. Final patient dose is calculated based on the date of injection and a Decay Correction Factor specific to number of days from the reference date affixed to the investigational vial to correct for physical decay.

10.1.1.2 NIST Standardization

The quantification of radium-223 radioactivity in Xofigo (radium-223 dichloride; BAY 88-8223) is based on the primary standardization performed by the US NIST. National Institute of Standards and

Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published[15].

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[15] and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of the re-assessment, NIST reported their findings[16] and had issued a revised NIST SRM in 2015. The discrepancy in the NIST standardization was determined to be −9.5% between activity values obtained using the old reference standard relative to the new primary standardization. Consequently, the current numerical values need to be corrected by approx. + 10.5%. The FDA has fully approved the regulatory variation submitted for Xofigo. The change in the numerical description of the patient's dose, product strength and labeled vial activity does not impact the safety or efficacy of Xofigo. The change in the NIST radium-223 standard has no impact on subjects; dose subjects are receiving, and will continue to receive. Subjects will receive the same actual dose and volume that was studied in Study 15245 (BC1-06 dosimetry study) and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard.

10.1.2 Mechanism of Action

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

10.1.3 General warning Ra-223

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

10.1.4 Radiation protection R-223

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

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

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

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

10.1.5 Dose calibration

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

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

10.1.6 Dosimetry

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

For an administered activity of 4.00 MBq (0.109 mCi) (55kBq (.0015▪ciper kg body weight to a 73-kg adult), the calculated absorbed doses to the bone (osteogenic cells) is 4.2050 Gy (420.5 rad) and to the red marrow is 0.5066 Gy (50.66 rad). The calculated absorbed doses to the main excretory organs are 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy (11.8 rad) for the upper large intestine wall and 0.1696 Gy (16.96 rad) for the lower large intestine wall.

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

The hematological adverse drug reactions observed in the clinical studies with Ra-223 are much lower in frequency and severity than what could be expected from the calculated absorbed doses to

the red marrow. This may be related to spatial distribution of alpha particle radiation resulting in non-uniform radiation dose to the red marrow.

10.1.7 Dose handling

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

10.1.8 Dose calculation

The dosage of Radium Ra 223 dichloride is 55 kBq/kg body weight. The patient dose is calculated based on date of injection, a decay correction (DK) factor specific to number of days from reference date applied to correct for physical decay of radium-223, and patient weight. A table with DK values according to physical decay of the study medication will be provided with every shipment of Radium Ra 223 dichloride.

Radium-223 is an alpha particle emitter with a physical $t^{1/2}$ of 11.4 days. The radioactive concentration at the reference date is 11,100 kBq/mL.

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

$$\frac{\text{Body weight (kg)} \times \text{dose (55kBQ/kg body weight)}}{\text{DK factor} \times 1100\text{kBq (0.0297·Ci)/mL}}$$

10.1.9 Dose preparation

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

10.1.10 Dose administration

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

10.1.11 Dose Modification

Every effort should be made to administer the full dosing regimen of Radium Ra 223 dichloride. Adjustment of dose level is not permitted.

Study visits during the treatment period should occur at intervals of at most 4 weeks (within a window of +/- 7 days). Dosing delays may be instituted under the following circumstances:

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

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

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

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

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

Any Other Toxicity:
Local practice will apply.

10.2 Docetaxel

10.2.1 Description

Docetaxel is commercially available. Docetaxel is an antineoplastic agent belonging to the taxoid family. Mechanism of action is antineoplastic, disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions.

10.2.2 Concurrent and Supportive Medications

Docetaxel will be administered in combination with prednisone 5mg twice daily and reduced or eliminated for toxicity at the discretion of the investigator.

The recommended pre-medication regimen is dexamethasone 8mg (PO or IV), 12 hours, 3 hours and 1 hour before the docetaxel infusion. However, other schedules are also acceptable if summary of product characteristics regimen is different to local practice.

Anti-emetic regimens are recommended as per local clinical practice.

10.2.3 Adverse Reactions

Most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

10.2.4 Warnings

10.2.4.1 Hepatic Impairment
Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with docetaxel.

10.2.4.2 Hematologic Effects
Perform frequent peripheral blood cell counts on all patients receiving docetaxel.

10.2.4.3 Hypersensitivity Reactions
Patients should be observed closely for hypersensitivity reaction, especially during the first and second infusions. This is characterized by generalized rash/erythema, hypotension, and/or bronchospasm, or very rarely fatal anaphylaxis.

10.2.4.4 Fluid Retention
Severe fluid retention has been reported following docetaxel. Patients should be premedicated with oral corticosteroids prior to each administration to reduce the incidence and severity of fluid retention.

10.2.4.5 Acute Myeloid Leukemia
Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide.

10.2.4.6 Cutaneous reactions
Localized erythema of the extremities with edema followed by desquamation has been observed.

10.2.4.7 Neurologic Reactions
Severe neurosensory symptoms (e.g. paresthesia, dysesthesia, pain) has been observed.

10.2.4.8 Eye Disorders
Cystoid macular edema has been reported.

10.2.4.9Asthenia
Severe asthenia has been reported. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration in performance status in patients with progressive disease.

10.2.4.10 Alcohol content
Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of docetaxel may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in docetaxel on the ability to drive or use machines immediately after the infusion.

10.2.5 Administration Precautions

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended.

10.2.6 Drug Interactions

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. Concomitant use of drugs that inhibit CYP3A4 should be avoided.

10.3 Drug logistics and accountability

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

10.3.1 Accountability

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

10.3.2 Destruction and Return

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

11 Trial Management

11.1 Data Safety Monitoring Board

The Tufts Cancer Center Data Safety Monitoring Board (DSMB) will provide data and safety oversight of this trial. A DSMB Charter will outline all activities of the board. Additionally, Tufts will submit data summary reports quarterly to the Data Safety Monitoring Board (DSMB) at participating sites. The DSMB will review the data every three months for additional safety monitoring. The DSMB will review investigators' assessments and decision-making regarding toxicities, SAEs, treatment-related or unrelated, and dose-limiting toxicity (DLT) assessments in the context of the target DLT rate specified in the study design. The DSMB will also review the investigators' determinations of dose-escalations within the specified Phase I design based on the DLT rates. Investigators will confer with the DSMB with regard to unexpected rates or severity of cumulative adverse events at any time during the course of the treatment, *i.e.* including those beyond Cycle 1 of combination therapy that may lead to a recommendation to discontinue the study based upon an estimated untoward risk to subjects receiving the study treatments.

11.2 Monitoring

Remote monitoring of trial sites will be conducted periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as

submitted via the data collection system. The site investigator and institution guarantee access to source documents by Tufts Medical Center or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Bayer or its designee.

It is important for the site investigator and their relevant personnel to be available during the remote monitoring visits and possible audits and for sufficient time to be devoted to the process.

12 Data Handling and Record Keeping

12.1 Case Report Forms and Submission

A case report form (CRF) is required and must be completed for each included subject. The completed dataset will be housed at Tufts Medical Center and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Tufts Medical Center. Case report form system, REDCap Cloud, is properly validated and compliant with FDA regulation 21 CFR part 11.

12.2 Record Retention

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 7 years following the completion of the study. ICFs and adequate records for the receipt and disposition of all study medications must be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA and other applicable Regulatory Authorities are notified, unless a longer period is required by applicable law or regulation. The Investigator must not discard any records unless given written authorization by the Sponsor.

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APPENDIX

STUDY SCHEDULE OF EVENTS[13]

Examination	**Screening**		**4 Week Lead-in**		**Combination Treatment**							**End Of Treatment**[9]	**Follow up for Progression Free Survival**[10]	**Follow Up for Overall Survival**[11]
	-28 days	-14 days	Day 1	Day 15	C1 D1	C1 D15 (and all further Day 15's)	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	4 weeks after last Ra223 treatment, prior to next therapy	Every 3 months until progression	
REQUIRED ASSESSMENTS														
Informed consent	X													
Diagnosis confirmation [1]	X													
Medical history		X												
Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs including ECOG PFS[2]		X	X	X	X	X	X	X	X	X	X	X		
AE, DLT and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	
REQUIRED LABORATORY TESTS														
CMP[3]		X		X	X	X	X	X	X	X	X	X	X	
CBC with differential and platelet		X		X	X	X	X	X	X	X	X	X	X	
Testosterone[4]		X						X[4]			X[4]	X[4]	X[4]	
PSA[5]		X			X		X	X	X	X	X	X	X	
SURVEYS														
FACT-P [6]		X			X			X		X		X	X[6]	
BPI [6]		X			X			X		X		X	X[6]	
DISEASE ASSESSMENT														
CT Chest, Abdomen, Pelvis[7]	X							X[7]			X[7]		X[7]	
Radionuclide Bone Scan[7]	X							X[7]			X[7]		X[7]	
TREATMENT EXPOSURE														
Docetaxel [12]			X	X	X	X	X	X	X	X	X			
Radium-223 [12]					X		X	X	X	X	X			
CORRELATIVE STUDIES														
Bone specific Alk Phos[8]		X			X			X		X		X		
Urine N-telopeptide[8]		X			X			X		X		X		
FOLLOW UP														
Follow Up												X[9]	X[10]	X[11]

Footnotes:

1. Diagnosis confirmation via pathology report from original or most current biopsy (completed locally).

2. Vital signs to include blood pressure, heart rate, temperature, weight, height (screen only) and ECOG performance status.

3. Complete Metabolic Profile (CMP) consists of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphate, alkaline phosphatase, aspartate aminotransferase (also known as SGOT or AST), alanine aminotransferase (also known as SGPT or ALT), total bilirubin, total protein, and albumin.

4. Testosterone will be done at screening, and every 12 weeks thereafter (e.g. C3D1 and C6D1) until disease progression.

5. PSA values will be checked at Screening, on Day 1 of every cycle, at EOT visit, and every 12 weeks in follow up until disease progression occurs.

6. FACT-P and BPI to be performed at Screening, C1D1, C3D1, C5D1 and End of Treatment and then every 12 weeks until disease progression or until starting a new line of therapy.

7. CT Scan and bone scan should be done at screening (within 28 days prior to starting protocol therapy). They will be repeated at C3D1, C6D1, and then every 12 weeks until progression (if treatment is discontinued before progression). Scans may be done at the discretion of the site investigator at any time for suspected progression. Scans should be performed +/- 7 days from the date they are due.

8. Correlative studies (bone specific alkaline phosphatase and urine N-telopeptide) will be performed at screening within 14 days of starting study treatment. They will be repeated at C1D1, C3D1, C5D1 and at EOT visit.

9. End of Treatment (EOT) visit: This will occur 4 weeks after last Ra223 dose. If AEs are present at EOT, they will be followed until resolution or initiation of new cancer therapy whichever occurs first.

10. Subjects who discontinue treatment for any reason (including completing the 6 cycles of planned therapy) without documented disease progression will be followed every 12 weeks for disease progression.

11. Once disease progression is documented, subjects will enter a survival follow up period every 3 months until death. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

12. All doses of docetaxel should be given +/- 3 days of the date they are due and all doses of Ra-223 should be given +/- 7 days of date due.

13. The assessments are the same in both the dose escalation and the expansion cohorts. However, as per Section 5.2.4, the expansion cohort will not open if the MTD is not identified from the dose escalation cohort.

FACT-G (Version 4)

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

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

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

FACT-G (Version 4)

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

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

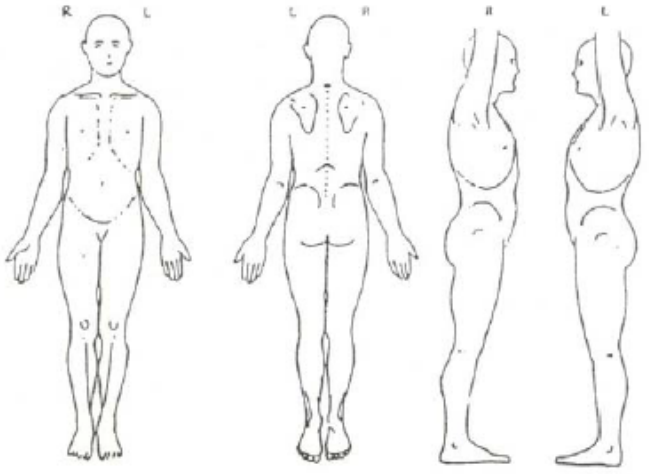
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping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

BRIEF PAIN INVENTORY

Date: _____

Name: _____

1. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts most.



2. Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

3. Please rate your pain by circling the one number that best describes your pain at its least in the last week.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain on average.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6. What treatments or medications are you receiving for your pain?

_____

_____

7. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that best shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No relief										Complete relief

8. Circle the one number that describes how, during the past week, pain has interfered with your:

a. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

b. Mood

0	1	2	3	4	5	6	7	8	9	10

c. Walking ability

0	1	2	3	4	5	6	7	8	9	10

d. Normal work (includes both outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10

e. Relations with other people

0	1	2	3	4	5	6	7	8	9	10

f. Sleep

0	1	2	3	4	5	6	7	8	9	10

g. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.