Phase I Dose Escalation of Monthly Intravenous Ra-223 dichloride in Osteosarcoma

Test drug(s):	Ra-223 dichloride (BAY 88-8223)		
Study purpose:	Proof of concept of targeted Ra-223-dichloride therapy for osteosarcoma, a bone-forming cancer		
Clinical study phase:	I/II		
Version no.:	6	Date:	13-Oct-2014
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Bayer Study no.:	**ONC-2012-66**		

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

Title	Phase I Dose Escalation of Monthly Intravenous Ra-223 dichloride in Osteosarcoma
Clinical study phase	Phase I/II
Study objective(s)	Primary objective: Determine maximum tolerated or recommended dose of monthly 223-radium dichloride in patients with recurrent or metastatic osteosarcoma. Comparison of safety and toxicity of 50, 75, and 100 kBq 223-radium dichloride /kg will be made. Secondary Objective: compare alkaline phosphatase reduction to quantitative imaging techniques (^{99m}Tc-MDP, ^{18}FDG-PET-CT, ^{18}FNa PET-CT scans to determine objective response of osteosarcoma indicator lesions to 223-radium dichloride
Name of active ingredient **Dose(s)** **Route of administration**	Ra-223 dichloride 50, 75 or 100 kBq/kg body weight Intravenous
Indication	Osteosarcoma recurrence or metastatic (bone-forming tumors)
Diagnosis and main criteria for inclusion	Osteosarcoma with 1) metastatic or recurrent disease and 2) indicator lesion(s) avid on ^{99m}Tc-MDP bone scan.
Study design	The study design is a 3+3 Phase I dose escalation (N=3/cohort) with expansion at highest safe dose (N=6); if 75kBq is 2/3 DLT, the dose -1 (50kBq/kg) is the MTD
Type of control	Uncontrolled study (i.e. no placebo or control group)
Number of subjects	Dose escalation N=14; dose expansion N=6 ;total= 20
Plan for statistical analysis	Primary objective: Determine maximum tolerated or recommended dose of monthly 223-radium dichloride in patients with recurrent or metastatic osteosarcoma. Comparison of safety and toxicity of 50, 75, and 100 kBq 223-radium dichloride /kg will be made. Secondary Objectives: Analysis change in objective measurements of alkaline phosphatase pre , before dose 4 (mid study) and at end of study (after dose 6) vs change in SUV of for PET- scans (18FDG and /or 18FNa) and of SPECT CT for ^{99m}Tc-MDP. Changes in uptake will be analyzed for dose response effects (between groups) and pre vs mid study and end of study (within group)

List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BPI-SF	Brief Pain Index (Short Form)
BSoC	Best Standard of Care
CBC	Complete Blood Count
CRO	Clinical Research Organization
CRPC	Castration Resistant Prostate Cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events; version 4.03
DK	Decay Correction Factor
EBRT	External Beam Radiation Therapy
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EU	European Union
GCP	Good Clinical Practice
GCL	Global Clinical Leader
GMP	Good Manufacturing Practice
HRPC	Hormone Resistant Prostate Cancer
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
IxRS	Interactive Voice/Web Response System (IVR/IVRS)
kBq	KiloBecquerel; SI Unit of Radioactivity
kg	Kilogram
LHRH	Luteinizing-Hormone-Releasing Hormone; also known as Gonadotropin-Releaseing Hormone (GnRH)
mCi	Millicuries
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PS	Performance Status
PSA	Prostate Specific Antigen
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SRE	Skeletal-related Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
WHO-DD	World Health Organization – Drug Dictionary

Definitions of terms

Ra-223 dichloride	The investigational product, a targeted alpha-pharmaceutical (a radiopharmaceutical emitting alpha radiation), is a ready-to-use solution for intravenous injection containing the drug substance radium chloride. The active moiety is the alpha particle emitting nuclide Ra-223, present as a divalent cation (223Ra2+).
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 Ra-223 dichloride administered.

1. Introduction

1.1 Background

Ra-223 dichloride is potentially a very low toxicity and high efficacy targeted agent for osteosarcoma, an osteoblastic bone-forming tumor. Because of low marrow toxicity of this radiopharmaceutical, knowledge of the MTD in this patient population is needed to develop future protocols. Use of Ra-223 dichloride in osteosarcoma should reduce the morbidity of therapy and mortality from metastases. The goal of this initial study is to determine the safety of escalating doses of monthly $^{223}RaCl_2$ in osteosarcoma patients with osteoblastic bone-forming metastases until MTD or a dose 100 kBq/kg dose is reached (whichever is first). Ra-223 dichloride will be given monthly and side effects of this bone-targeted therapy on monthly blood counts and alkaline phosphatase will be determined. After 3 and 6 doses patients will have imaging to compare ^{99m}TcMDP uptake to baseline and other imaging as clinically indicated including ^{18}F-FDG PET-CT , Na^{18}F and/ chest CT. Evaluations will include anatomic imaging (CT or MRI) of all sites of disease along with chest CT at baseline and restaging for all patients to allow for assessment of RECIST progression. RECIST progression will determine progressive disease regardless of other imaging. If well tolerated at the MTD, an additional 6 patients will be studied to better define toxicity and obtain data to support future investigation of Ra-223 dichloride with other agents and modalities (e.g. other drugs, surgery or external beam RT) for improved treatment of osteosarcoma.

1.2 Rationale of the study

Patients with osteosarcoma recurrence or metastases after initial therapy have 5 year overall survival of 16%. The median survival after 1st, 2nd, 3rd, or 4th recurrence was about 1 year [1] Although chemotherapy may possibly contribute to longer overall survival after first relapse, surgery is critical to prevent subsequent relapses. Thus for patients with axial, recurrent, or metastatic osteosarcoma, more effective treatments are needed. Ra-223 dichloride is an alpha-emitting radiopharmaceutical developed by Oyvind Bruland at the Norwegian Radium Hospital in Oslo (figure 1).

The intrinsic bone targeting property of Ra-223 dichloride is similar to calcium and other alkaline earth elements. Tables 2 and 3 show how the ^{223}Ra alpha-particle emitting radiopharmaceutical has different radiation dose characteristics than the current FDA approved beta-emitting radiopharmaceuticals such as $^{89}SrCl_2$ and ^{153}Sm-EDTMP [2]. Despite experience with ^{153}Sm-EDTMP for treatment of high-risk osteosarcoma [3-8], Radium-223 dichloride may have very significant advantages (less marrow toxicity and repeated dosing without stem cell support possible) compared to ^{153}Sm-EDTMP. Radium-223 dichloride emits alpha-particles with high energy and high linear energy transfer (LET) radiation with a range limited to less than 100 micrometers. These radiation characteristics have the advantages of generating highly localized and effective radiation kill zones via the high probability of the dense alpha particles inducing double-strand breaks to the DNA of cancer cells.

In contrast, the ^{89}Sr and ^{153}Sm emit beta-particles (electrons) that have much lower energy and lower LET. Beta radiation mainly induces single-strand breaks to DNA which are more easily repaired. In addition, beta-particles typically have 30-80 times longer radiation range compared to alpha-particles. Thus, nearby tissues are more subject to collateral damage from beta-emitters. For example after radiation from beta-emitters, nearby marrow and stem cells are damaged resulting in anemia, leucopenia, and thrombocytopenia.

Rationale for dose level being studied

Ra-223 has been extensively studied in prostate cancer, with a median age of > 65. Osteosarcoma occurs in adolescent and young adults and for this type of disease, an osteoblastic bone-forming tumor, perhaps a higher dose would have a better efficacy in terms of its direct bone targeting properties. Because of low marrow toxicity of this radiopharmaceutical, knowledge of the recommended dose in this patient population is needed to develop future protocols.

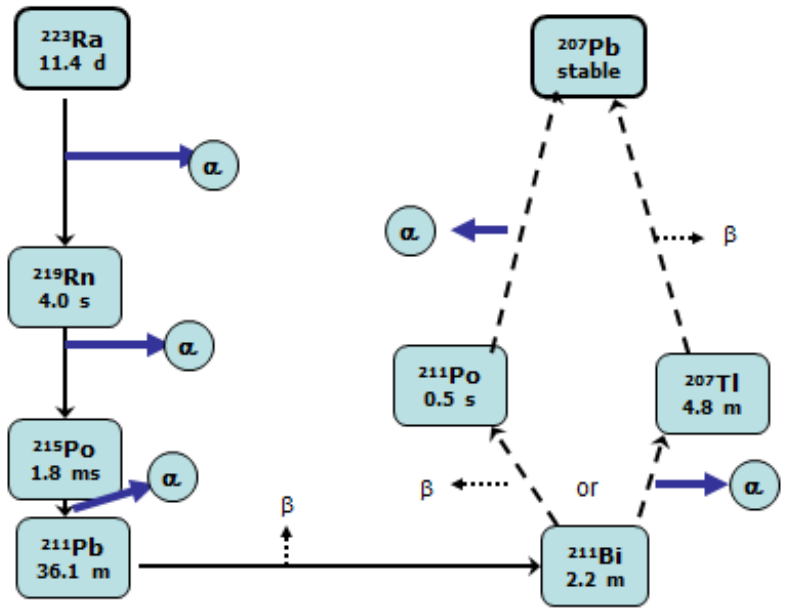

Figure 2. Decay cascade of Ra-223. The initial ejection of the high LET alpha particle takes a relatively long time (t=11.4 days). Subsequent quick decay of radon daughters provide additional alpha particles quickly with for increased therapeutic effectiveness at target location of emission (bone-forming tumor cell in the case of osteosarcoma) and little changece for diffusion of radon daughters to other locations/tissues for non-target effects.

1.3 Ra-223 dichloride

1.3.1 Preclinical

In single and repeated dose toxicity studies in rats, the main findings were reduced body weight gain, hematological changes, reduced serum alkaline phosphatase and microscopic findings in the bone marrow (depletion of hematopoietic cells, fibrosis), spleen (secondary extra-medullary hematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line). These findings were related to radiation-induced impairment of hematopoiesis and a reduction of osteogenesis and occurred beginning in the dose range of 20 (0.00056 mCi) – 80 kBq (0.0022 mCi) per kg body weight, with the exception of body weight decreases. [1] [2]

Dose-limiting myelotoxicity was seen in dogs after single administration of 450 kBq (0.012 mCi) Ra-223 dichloride per kg body weight (9 times the clinically recommended dose).

Osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses in rats 7 – 12 months after start of treatment. Osteosarcomas were not observed in dog studies. No case of osteosarcoma has been reported in clinical studies with Ra-223 dichloride. The risk for patients to develop osteosarcomas with exposure to Ra-223 dichloride is unknown at present.[3] [4] [5]

Studies on reproductive and developmental toxicity have not been performed. Since Ra-223 dichloride binds to bone, the potential risk for toxic effects in the male gonads in cancer patients with castration-resistant prostate cancer is very low, but cannot be excluded. Studies on the mutagenic and carcinogenic potential of Ra-223 dichloride have not been performed
.

No histological changes were observed in organs involved in the excretion of Ra-223 dichloride. No significant effects were seen on vital organ systems, i.e. cardiovascular (dog), respiratory or central nervous systems (rat), after single dose administration of 450 to 1000 kBq (0.012 to 0.027 mCi) per kg body weight (9 (dog) to 20 (rat) times the clinically recommended dose.

1.3.1 Pharmacokinetics / pharmacodynamics

No PK or PD studies are proposed. See Investigator's brochure.

1.3.2 Clinical Experience Summary

The clinical development of Ra-223 dichloride, to date, includes nine studies in patients with prostate cancer or breast cancer with bone metastases. The Phase I program consisted of three studies to establish the safety, dose limiting toxicities, dosimetry, biodistribution and PK in patients with bonemetastases mainly from prostate cancer; and it included some patients with MBC with bone metastases. The Phase II program included three completed studies of Ra-223 dichloride in patients with prostate and breast cancer, who have bone metastases. The results of the completed studies indicated that safety and tolerability of Ra-223 dichloride in CRPC/HRPC patients with bone metastases was well tolerated, and that there was evidence of dose related efficacy against bone markers and other markers of disease. In addition there was an effect on median overall survival in a Phase II (BC1-02) placebo-controlled study. These studies enabled the initiation of the Phase III ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) study.

The clinical safety and efficacy of Ra-223 dichloride have been evaluated in a double-blind, randomized, multiple dose, phase III multicenter study (ALSYMPCA) in castration-resistant prostate cancer patients with bone metastases. The primary efficacy endpoint was Overall Survival (OS).

At the cut-off date of the pre-planned interim analysis, a total of 809 patients were randomized 2:1 to receive Ra-223 dichloride 50 kBq (0.0014 mCi)/kg intravenously every 4 weeks for 6 cycles (N=541) plus best standard of care or matching placebo plus best standard of care (N=268). Best standard of care included e.g. local external beam radiotherapy, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole.

An updated descriptive analysis of safety and of OS was performed in 921 randomized patients prior to implementing crossover (i.e. offering patients in the placebo group to receive Ra-223 dichloride treatment).

The results of both, interim and updated analysis, revealed that OS was significantly longer in patients treated with Ra-223 dichloride plus best standard of care compared to patients treated with placebo plus best standard of care. For the updated analysis, an increase in median overall survival of 3.6 months was seen with Ra-223 dichloride plus best standard of care compared to placebo plus best standard of care (HR =0.695 (95% CI 0.581/0.832), median OS 14.9 months versus 11.3 months, respectively).

The results of the interim analysis and the updated analysis showed also a significant improvement in all main secondary endpoints in the Ra-223 dichloride arm compared to the placebo arm:

Time to SRE (to be update based on final results) - *As with good practice, the sponsors have conducted further verification of the ALSYMPCA SRE data in preparation for the US FDA NDA regulatory submission. This has resulted in changes in the numbers previously reported for SRE data in the ASCO 2012 abstracts (Abstract #4551, LBA #4512). Though discrepancies were noted, the overall interpretation of the results has not changed. The SRE data will be disclosed once all additional data verification and analyses activities are completed."*

Prolonging the time to total ALP progression (defined as ≥ 25% increase compared to baseline/nadir) (Interim analysis: HR = 0.163, 95% CI 0.121 – 0.221; p < 0.00001, median number of months not estimable since median was not reached at the time of data cut-off; updated analysis: HR = 0.167, 95% CI 0.129 – 0.217; median number of months = 7.4 months for Ra-223 dichloride versus 3.8 months for placebo).

Time to PSA progression (defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir) was also

significantly prolonged in patients receiving Ra-223 dichloride compared to patients receiving placebo (Interim analysis: HR = 0.671, 95% CI 0.546 – 0.826; p = 0.00015, median number of months = 3.6 months for Ra-223 dichloride versus 3.4 months

Total ALP response (confirmed ≥ 30% reduction compared to baseline) at week 12 compared to the placebo group (Interim analysis: 43.3% in the Ra-223 dichloride group, 2.5% in the placebo group, p < 0.001; updated analysis: 46.9% in the Ra-223 dichloride group, 3.3% in the placebo group).

Most common non-hematologic all grades adverse events occurring in more than 15% of patients were: bone pain (43% vs. 58%), diarrhea (22% vs. 13%), nausea (34% vs. 31%), vomiting (17% vs. 13%) and constipation (18% vs. 18%). Most common hematologic all grades adverse events were anemia (27% vs. 27%), neutropenia (4% vs. 1%) and platelets (8% vs. 6%).

Subgroup survival analysis

Subgroup survival analysis showed a consistent survival benefit for treatment with Ra-223 dichloride, independent of total alkaline phosphatase (ALP), current use of bisphosphonates, prior use of docetaxel and baseline ECOG status.

Pain relief

The results from the phase III ALSYMCA study regarding time to external beam radiation therapy (EBRT) for pain relief and fewer patients reporting bone pain as an adverse event in the Ra-223 dichloride group indicate a positive effect on bone pain. This is further supported by the effects seen on bone pain using specific pain measures in a single dose Phase II study.

2. Study objectives

2.1 Primary Objective: Determine maximum tolerated or recommended dose of monthly Ra-223 dichloride in patients with recurrent or metastatic osteosarcoma. Comparison of safety and toxicity of 50, 75, and 100 kBq Ra-223- dichloride /kg will be made.

2.2 Secondary Objectives: compare alkaline phosphatase reduction to quantitative imaging techniques (^{99m}Tc-MDP, ^{18}FDG-PET-CT, ^{18}FNa PET-CT scans to determine objective response of osteosarcoma indicator lesions to 223-radium dichloride

3. Investigator[s] and other study participants

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4. Study design

The goal of this initial study is to determine the safety of escalating doses of monthly Ra-223 dichloride in osteosarcoma patients with osteoblastic bone-forming metastases until MTD or a dose 100 kBq/kg dose is reached (whichever is first). Radium-223 dichloride will be given monthly for up to 6 cycles and side effects of this bone-targeted therapy on monthly blood counts and alkaline phosphatase will be determined. After 3 and 6 doses patients will have imaging to compare ^{99m}TcMDP uptake to baseline and other imaging as clinically indicated including ^{18}F-FDG PET-CT , Na^{18}F and/ chest CT. Anatomic imaging (CT or MRI) of all sites of disease along with chest CT at baseline and restaging for all patients will be done to allow for assessment of RECIST progression. RECIST progression will determine progressive disease regardless of other imaging.

Table 1. Ra-223 dichloride Dose Escalation scheme (N=3/cohort)

Dose level:	kBq/kg	N
-1	25	--
0 (starting dose)	50	3
1	75	3
2	100	8
Expansion cohort	MTD	6

Anticipated Total N = 9- 20 (N= 20 assumes reaching 100 mBq/kg MTD)

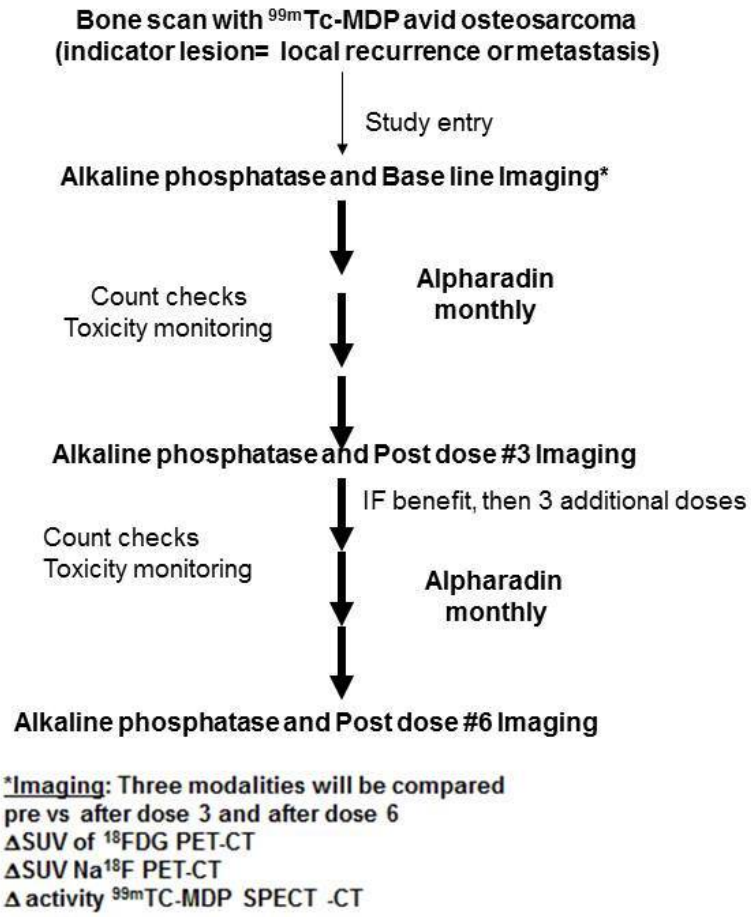

Table 2. Decay and Marrow/Bone Ratios Clinically Useful Bone-seeking Isotopes

	Half-life Days	*Ratio of Surface Bone : red marrow	Particle	MeV particle Emission energy	Range (mm)
^{153}Sm-EDTMP	2	4.4	Beta	0.66 max 0.22 average	0.6
$^{89}SrCl_2$	50.5	1.6	Beta	0.58	2.4
^{223}RaCl	11.4	10.3	Alpha	27.4	<0.1

* Bone surface to red bone marrow radioactivity dose ratio

Table 3. Comparison of Alpha and Beta Particles from Bone-Seeking Cancer Drugs

Characteristic	Alpha	Beta
Range (um)	40-90	50-6000
Linear Energy Transfer*	60-230	0.015-0.4

Relative mass	7000**	1**
DNA hits to kill a cell	1-5	100-3000
Cytotoxic against G_0 cells	Yes	No
Effective against “radio-resistant” cells	Yes	No

*(LET; keV/μm)
**Alpha particles are dense particles (i.e. like a helium nucleus); beta particles are electrons
Preclinical work showed that mice had significantly less marrow toxicity from Ra-223 dichloride than after the beta-emitting radiopharmaceutical strontium-89 chloride [9, 10]. Alpharadin has shown promising marrow-sparing properties in patients with bone metastases of hormone refractory prostate cancer [2, 11, 12]. In a placebo controlled trial, patients with hormone refractory prostate cancer bone metastases had no significant effects on blood counts after repeated monthly Ra-223 dichloride doses (50kBq/kg) [12].

Bone marrow suppression from Ra-223 dichloride has been minimal. Alkaline phosphatase in patients with prostate cancer bone metastases after ^{223}Ra decreased was 66% versus increase of 9% in placebo treated patients (p=0.001) [12] Time to PSA progression was 26 versus 8 weeks (p=0.048). A large phase III multicenter, randomized, double blinded, placebo controlled trial in prostate cancer is underway and includes centers in Europe and the USA [13]. Results of Alpharadin against prostate cancer bone metastases in two randomized phase II studies were reviewed at ASCO 2011 by Nielsson et al. [14]. Alkaline phosphatase normalization was dose-related in trial BC1-04: 5/29 (17% in 25 kBq/kg group, 10/25 (40%) in the 50kBq/kg group, and 10/21 (48%) in the 80 kBq/kg group. Alkaline phosphatase normalization was associated with significantly improved median survival (58 weeks vs 102 weeks (log rank p=0.0086).

Alkaline phosphatase is a marker not only of bone formation associated with metastases to bone in osteosarcoma, but also the intrinsic bone forming activity by the osteoblastic osteosarcoma neoplastic cells. Mialou et al. found that not only bone (vs lung) metastases, but also high alkaline phosphatase (>500 IU) was significantly associated with a worse outcome in metastatic osteosarcoma [15]. An alpha-emitting targeted radiopharmaceutical located in osteosarcoma target tissue will deliver the radiation to a much more localized tumor volume than a beta-emitter, thereby reducing exposure of surrounding normal tissues and leading to less toxicity.

Thus a dose finding study to determine best dose for monthly Alpharadin dosing in osteosarcoma is proposed. This information can then be used to develop potential “game-changing” strategies against osteosarcoma to improve pain in metastatic patients, make surgery better (fewer amputations, better function), and reduce the considerable morbidity of current therapy,

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

- Patients with progressive, locally recurrent, or metastatic osteosarcoma (i.e. high-risk only) with no standard curative options available with at least one indicator lesion avid on 99mTc-MDP scan or a Sodium Fluoride (Na F) Bone PET scan will be eligible. In addition, subjects with extremely rare bone forming osteosarcoma-like tumors that behave like osteosarcoma phenotypically and are clinically treated like osteosarcoma (eg. Malignant Fibrous Histiocytoma of Bone or malignant transformation of giant cell tumor of bone) may be included if they satisfy all of the inclusion criteria.
- Anatomic imaging (CT or MRI) of all sites of disease along with chest CT at baseline and restaging for all patients will be done to allow for assessment of RECIST progression. RECIST progression will determine progressive disease regardless of other imaging.

- Indicator lesion that has uptake of ^{99m}Tc-MDP on bone scan or a Sodium Fluoride (Na F) Bone PET scan and can be subjected to quantitative assessment by this scans and possibly other means
  - Age 15 and above and >40 kg.
  - ECOG=2 or better
  - Subjects or their guardians must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
  - All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF).
  - Women of childbearing potential must have a negative serum or urine pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
  - Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 30 days after the last dose of study drug. The definition of adequate

contraception will be based on the judgment of the principal investigator or a designated associate.

- Acceptable hematology and serum biochemistry screening values:
    - White Blood Cell Count (WBC) ≥ 1500/mm3
    - Absolute Neutrophil Count (ANC) ≥ 1,000/mm3
    - Platelet (PLT) count ≥ 75,000/mm3
    - Hemoglobin (HGB) ≥ 8 g/dl
    - Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
    - Creatinine ≤ 1.5 x ULN
    - Albumin > 25 g/L
- Willing and able to comply with the protocol, including follow-up visits and examinations

5.1.2 Exclusion criteria

- Diagnosis other than osteosarcoma
- ^{99m}Tc-MDP bone scan with no significant uptake (i.e. “nothing” for a bone-seeking isotope to target/ i.e. indicator lesion that would be expected to have the bone-seeking targeted uptake of 223-radium dichloride)
- Other malignancy treated within the last 3 years (except non-melanoma skin cancer or low-grade superficial bladder cancer)
- Any other serious illness or medical condition, such as but not limited to:
    - Any active infection ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 Grade 2
    - Cardiac failure New York Heart Association (NYHA) III or IV
    - Fecal incontinence (this is because of Ra-223 elimination in feces)
- Women who are pregnant or breast-feeding.
- Inability to comply with the protocol and/or not willing or not available for follow-up assessments.

- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization)
- Patients on oxygen

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Progressive disease and dose limiting toxicity (DLT)
- Subject is lost to follow-up.
- Death.

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

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.

- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

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

5.2.2 Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has already been assigned to treatment and administered at least one dose of study drug.

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

5.2.3 Replacement

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons or disease progression) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made by the study investigator. Both the replacement and originally allocated number will be unique numbers.

6. Treatment

6.1 Treatments to be administered:

Monthly doses of Radium-223-dichloride

6.2 Treatment assignment

Patients will be screened with clinically appropriate tests for study inclusion. A patient number (a unique identification number from CORe in MD Anderson) will be assigned after a patient is evaluated for inclusion into the study and signs informed consent after successful screening.

6.2.1 Radium-223 dichloride

6.2.2 Treatments to be administered

Ra-223 dichloride will be administered as a slow bolus IV injection at intervals of every 4 weeks for up to 6 cycles.

- Dose (50, 75, or 100 kBq/kg) will be assigned in cohorts of 3 after study registration in CORe.
- Dose #1 should be given within 30 days of study registration
- At least 3 patients will be required to successfully complete 6 weeks of therapy before advancing to the next cohort.
- Patients will receive the same Ra-223-dichloride dose as dose #1 for all subsequent doses.
- Monthly dosing (q 4 weeks +/- 6 days) as slow iv bolus for up to a total of 6 doses
- Monthly doses will be delayed, but no more than 2 weeks from scheduled dose for any grade 3 hematologic toxicity.

Criteria for subsequent doses (i.e. doses 2-6):

- Hematologic Toxicity (if present): Hb, ANC, and platelets- resolved to grade 2 or less within 6 weeks of prior dose. Since lymphopenia may be chronic, this will not be a criteria for subsequent doses
- All toxicities must be resolved to grade 2 or less in order to begin subsequent cycles
- Performance status ECOG 0 to 2
- Alkaline phosphatase stable or improving at the discretion of the treating physician
- Not on oxygen
- Not pregnant
- After dose #3 and before dose #4: stable disease or better in indicator lesions as determined by quantitative nuclear medicine imaging (^{18}FDG PET-CT, quantitative ^{99m}Tc-MDP SPECT/CT, or Na^{18}F PET/CT) or RECIST criteria on anatomic imaging (note: often osteosarcoma “indeterminate” lesions 1-9 mm remain stable or have minimal change depending on chest CT technique).
- Anatomic imaging (CT or MRI) of all sites of disease along with chest CT at baseline and restaging for all patients will be done to allow for assessment of RECIST progression.
- RECIST progression will determine progressive disease regardless of other imaging.

For the Phase I aspect of the protocol, prior to advancing/changing dose levels, a cohort summary must be completed and submitted to the Clinical Research Monitor in the IND Office.

6.2.3 Identity of study treatment

The alpha-pharmaceutical Ra-223 dichloride is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of Ra-223 dichloride for IV administration. Ra-223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0-8.0. The radioactive concentration at the reference date is 1000 kBq/mL. The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table.

Bayer Corporation will provide Ra-223 dichloride, which will be manufactured by the contract manufacturer: Institute for Energy Technology, Isotope laboratories, Kjeller, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. 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 MBq at the calibration 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.

6.2.4 Dosage and administration

Written information about Ra-223 dichloride and instruction about handling and injection of radioactive material will be provided to study personnel.

In general, the administration of radioactive drugs involves a potential risk for third parties, due to radiation from the patient and due to possible contamination by spilling urine or feces. When Ra-223 dichloride has been injected intravenously into a patient, the risk for external radiation exposure to third parties is extremely low, due to the short range of the alpha particles (<100 µm) and the low portion of beta and gamma radiation. For these

reasons the product can be administered on an out-patient basis. To minimize the risk of contamination, the patient and his caregivers will receive oral and written instructions regarding hygiene precautions to abide by after receiving the radioactive drug.

6.2.5 Dose calibration

Ra-223 dichloride can be measured in a normal dose calibrator instrument. When written approvals for the use of Ra-223 dichloride from the Radiation Protection Agency for the specific center have been received by the sponsor, a vial of 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 Ra-223 dichloride dial setting on their relevant dose calibrator(s). For dial setting, the clinical study center will receive a sealed vial containing a Ra-223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. The amount of 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.

6.2.6 Dose handling

The 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. 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 Ra-223 dichloride. Control measurements of both the Ra-223 dichloride vial (before and after dispensing) and syringes (before and after administration) are performed as part of the clinical trial documentation. All administrations of Ra-223 dichloride are based on the certified activity of Ra-223 dichloride at the calibration date.

6.2.7 Dose calculation

The dosage of Ra-223 dichloride is 50, 75, or 100 kBq/kg body weight. The total activity to be injected will be calculated volumetrically using the patient's body weight on the day of injection (kg), the 50 kBq/kg body weight dosage level, and the decay correction factor (DK) to correct for physical decay of Ra-223 dichloride. A table with DKs according to physical decay of the study medication will be provided with each vial of Ra-223 dichloride. The total amount (volume to be drawn into the syringe) to be administered to a patient should be calculated as follows:

Body weight (kg) x50 kBq/kg = volume to be injected (mL)
DK x 1000 kBq/mL

Data regarding activity should be recorded on the appropriate electronic case report form (eCRF) page.

6.2.8 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 usage of shielded syringes is strongly recommended; however, this decision will be dictated by the individual guidelines of the respective nuclear medicine department. Filling of the syringe should take place in a safety bench or similar cabinet in the Radiopharmacy/ Nuclear Medicine department. 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. Ra-223 dichloride should not be diluted or mixed with any solutions. 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.

6.2.9 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 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 slow bolus intravenous (IV) injection. 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 hospital procedure for the handling of radioactive material. Written information about Ra-223 dichloride and instruction about handling and injection of radioactive material will be given to study personnel

Radiation Safety Considerations
Radiation Risk Management for Patients
Biodistribution of ^{223}Ra in the body
Pharmacokinetics, biodistribution and dosimetry in man have been previously investigated (see also ATI-BC-1: blood pharmacokinetics; BC1-05: pharmacokinetics, biodistribution and radiation dosimetry; Algeta ASA). After intravenous injection of 2Ra-223 dichloride, then radiopharmaceutical is quickly eliminated from blood, taken up in bone and excreted via the small intestine. The major route of elimination is through the gut with the feces; at 48 hours only 1-5% was excreted in urine and the rate of urinary excretion was decreasing. Thus, the kidneys, urinary bladder, and urethra are exposed to a minimal amount of radiation.

Gamma scintigraphy images show early activity in the gut, decreasing at the later images. It is not possible to determine the relative activity within gut wall versus gut contents from the scan, but it is assumed that the activity is mainly confined to the gut contents (i.e. fecal stream). This is a reasonable assumption since the activity in the scans is seen to move along the gut. No specific uptakes were seen in any other normal organs such as the heart, the liver, the kidney, the gallbladder, stomach and the spleen. The highest absorbed doses were measured in the bone with lesser amounts in the red marrow.

Biosampling (blood tests)
In the first week after injection of Ra-223 dichloride, there may be radioactivity in body fluids. A considerable fraction of the study drug is eliminated via feces, and to a lesser degree via urine. Blood clearance after injection is very rapid (<1% remaining 24 hours post injection). To ensure radiation protection for hospital personnel, special attention should be directed to ensure that only necessary samples of blood, urine and feces should be handled during the first week after administration. In case of necessary unforeseen blood samples, laboratory personnel should be notified in order to avoid contamination. All patients in clinical trials with Ra-223 dichloride receive a card stating that they have received a radioactive drug and that special care should be taken during unforeseen contact with medical or public health services.

Restrictions for patients
Unlike many other radiopharmaceuticals, there are no restrictions on family contact after administration of Ra-223 dichloride. The range of α-particles in human tissue is £ 0.1 mm. Once injected, both α- and β-particles emitted from Ra-223 are stopped by the patient's tissue. Due to attenuation in the patient's body mass, the radiation outside the patient's body is extremely low and there should be no safety issues related to homeland security/airport travel. Nevertheless patients should have a letter or card indicating recent treatment with a radioisotope in case of detection in by radiation detectors while traveling (advice: wear clean underpants!). Dose rates (μSv/h per MBq injected) measured outside the body are ~200 at one centimeter and 0.02 at one meter[16]

Ra-223 dichoride can be given on an out-patient basis, and there are no restrictions on normal interactions with friends or relations. Patients are provided with written instructions describing simple steps to be followed at home in connection with vomit, blood, urine or stools for a period of one week after dosing.

Burial and Cremation risks
After burial 223Ra will decay naturally and has essentially no health risk to others after 3 months. Cremation of a body containing 223Ra does not present a significant risk to the local population or to the crematorium workers themselves, even if the worst case scenarios are assumed. When crematorium workers receive a body that contains any type of radioactivity, they should be suitably trained, informed

beforehand and given suitable personal protection equipment (i.e. universal blood and body fluid precautions - especially when handling ashes containing potentially radioactive bone fragments. Calculations and the rationale for radiation dose estimates are available upon request (see investigators Brochure).

Definition of Dose-Limiting Toxicities (DLTs):

Toxicities will be graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (publish date 28-May-2009). Dose-limiting toxicities include all adverse experiences that are related to study medication, and clearly not related to disease progression or intercurrent illness.

Based on prior experience with other bone seeking radiopharmaceuticals and Ra-223 dichloride in prostate cancer patients, the expected dose limiting toxicity (DLT) will be hematologic. Lymphopenia is common in patients with bone metastases and will be monitored, but not considered a DLT in this protocol. Any grade 4 anemia, any grade 4 neutropenia for >7 days or grade 4 neutropenia with fever (a single temperature greater than 38.3˚C or a sustained temperature of ≥ 38˚C for more than one hour) and grade 3 or 4 thrombocytopenia with clinically significant bleeding will be dose limiting. Grade 3 non-hematologic toxicities except for nausea, emesis or diarrhea that are controlled with maximal medical management within 72 hours will be considered dose-limiting. DLTs will only be monitored during the first 6 weeks of treatment. Ongoing toxicity that causes a delay of more than 2 weeks in starting the next cycle will also be dose-limiting if it occurs during the first cycle.

Dose Modification and Escalation

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

- A minimum of 3 patients initially will be enrolled at the first dose level.
- If at least 2 patients are observed to have a dose-limiting toxicity (DLT), the MTD will have been exceeded and no further patients will be enrolled at this dose level or at any higher dose level. The prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).
- If 0 of the 3 patients are observed to have DLT during the DLT assessment period, the dose level is escalated one step for the next cohort of 3 patients, and the process continues as above.

- If exactly 1 of the 3 patients treated show DLT during the DLT assessment period, 3 additional patients are treated at the current dose level.

- If none of these additional 3 patients show DLT during the DLT assessment period, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).

- A tentative MTD becomes final when a total of 6 patients are treated with less than 2 showing DLT.

- If 2 of the first 3 patients have hematologic DLT, then next cohort will be dose level -1.

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

Disease progression:

The Investigator should delay cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy or other investigational drug until the follow-up period. If such treatments have to be given during the treatment period, further study drug administrations must be discontinued. Patients with disease progression may continue other treatment at the Investigator's discretion.

Myelosuppression:

Treatment-related changes in hematology parameters may occur.

- Blood transfusion is acceptable between study drug administrations. Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity.

- If myeloid growth factors are required for the management of acute toxicity this event should be considered a DLT.

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.

For any grade 3 hematologic toxicity for >14 days, study drug administrations must be discontinued (grade 4 events of anemia and neutropenia >7 days are dose-limiting).

Spinal Cord Compression:

If the patient experiences spinal cord compression during the treatment period, the patient should be treated for the event, and this will be considered disease progression.

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.

6.3 Drug logistics and accountability

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

6.3.1 Accountability

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

6.3.2 Destruction and Return

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

6.4 Treatment compliance

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

6.5 Prior and concomitant therapy-

During treatment, all concomitant medications (including start/stop dates and indication) must be recorded in the patient's medical record and case report form (DMI)

Permitted

- Treatment with non-conventional therapies (e.g., herbs [with the exception of St. John's Wart], acupuncture) and vitamin/mineral supplements is acceptable provided that, in the opinion of the investigator, such treatment will not interfere with the trial endpoints.
- Subjects may receive standard of care for any underlying illness.
- In the event of neutropenia, anemia, or thrombocytopenia, subjects may receive appropriate supportive care (e.g., transfusion, biologic response

modifiers such as G-CSF or GM-CSF, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). This supportive care should not substitute a recommended dose modification.

- Blood transfusions and erythropoietin are allowed during the study period
- If surgery is required during study drug treatment, the surgeon needs to be notified that the patient has been treated with a radioactive product and adequate precautions for radioactive protection should be applied during the surgical procedure. The patient should continue with study treatment if considered safe in the treating Investigator's opinion.

7. Procedures and variables

7.1 Schedule of procedures

Labs and imaging are to be done no more than 28 days prior to registration and <30 days before dose#1 of study drug.

CBC every 2 weeks for the first 2 cycles (±7 days), then monthly or more frequently as clinically indicated. Monitoring of hematologic toxicity will be done with monthly cbc from that point on. Weekly testing will be recommended for any patients on a clinically indicated basis if they have symptoms suggesting anemia (e.g. increased fatigue or headaches), thrombocytopenia (e.g. petechiae, bruising) or neutropenia (fevers or infection). If clinically indicated (e.g. grade 3 or higher anemia, neutropenia or thrombocytopenia, hematologic monitoring may be done more frequently.

Alkaline phosphatase will be monitored monthly. Laboratory monitoring and imaging are summarized in table 4.

Blood counts may be done by local physician as clinically indicated and also week before anticipated dosing and communicated to study team to make sure patient is ready for dosing prior to travel to MD Anderson Cancer Center.

Pregnancy test will be required when applicable prior to every cycle.

7.1.1 Tabulated overview

Table 4 summarizes required labs and imaging.

Table 4: **Ra-223 dichloride for Osteosarcoma**: **observations/monitoring**

Test/Procedure	Before entry	Doses 2-6	After dose 3+ imaging	1 month after dose (end of study±7 days)

Physical exam (including vital signs and performance status+BPS[$])	x	x		x
CT/MRI Scans[+]	x		x	x
Nuclear Scans*	x		x	x
CBC[**] w diff	x	x	x	x
Creatinine	x		x	x
Bilirubin	x		x	x
ALT	x		x	x
Alk Phos	x	x	x	x
HCG**	x	x		
OSTEO[1]	x	x	x	x
BONE ALK[2]	x	x	x	x
CTX[3]	x	x	x	x
Pathology	x			

Nuclear scans: *bone scan required, Other imaging of indicator lesion(s): best study or studies for quantitative comparison after dose 3 and after dose 6 (e.g. LD of bone forming lesion on CT/MRI, or SUV on ^{18}FDG-PET-CT, or SPECT with ^{99m}Tc-MDP bone scan, or Na^{18}F PET).
[$]Brief Pain Survey.
[+]Evaluations to include anatomic imaging (CT or MRI) of all sites of disease along with chest CT at baseline and restaging for all patients will be done to allow for assessment of RECIST progression. RECIST progression will determine progressive disease regardless of other imaging.
HCG: Urine pregnancy test must be done within 7 days prior to start of study drug and when applicable prior to every cycle. Note serum HCG can be a false positive marker occasionally in osteosarcoma. For patients with a positive test result, pregnancy will be excluded by ultrasound.
**CBC w/diff: CBC every 2 weeks (±7 days) for the first 2 cycles, then monthly or more frequently as clinically indicated
1 Osteoclacin
2 Bone specific alkaline phosphatase
3 Serum CTX

Timing of assessments
Assessments are to be done monthly as indicated in table 4.

7.1.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.4.1.1.

7.2 Efficacy

Efficacy will be determined by
A) Trends comparing measurements of the indicator lesions using quantitative nuclear medicine scan will be used as exploratory end points. RECIST progression will determine progressive disease regardless of other imaging.
B) Alkaline phosphatase trends comparing before, after 3 doses and after 6 doses of Ra-223 dichloride

7.3 Pharmacokinetics / pharmacodynamics

7.4 Safety and Toxicity Monitoring

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

All observations pertinent to the safety of the study treatment will be recorded and included in the final report. Serious Adverse Events and/ any unexpected ***and*** clinically significant grade 3 or 4 toxicities will be reported to the MD Anderson IRB and Bayer. This trial will use the NCI-CTCAE v4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

7.4.1 Adverse events

Investigators should refer to the Safety Information section of the current IB for radium-223-dichloride, including the DCSI (development core safety information), for the expected side effects of Radium-223 dichloride. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

All concomitant medications must be recorded in the subject's medical record at each clinic visit (ClinicStation) .

Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment.

7.4.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE if the condition worsens compared to baseline).

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. phantom pain).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of 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.

7.4.1.2 Classifications for adverse event assessment

- Study treatment action
- Other specific treatment of AE
- Causal relationship to protocol-required procedures(s)
- Outcome

All unexpected and related grade 3 and 4 AEs will be assessed and documented in the MDACC AE log by the investigator according to the categories detailed below.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

7.4.1.2.1 Seriousness

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

For each AE, the seriousness must be determined according to the criteria given in Section 7.4.1.1.

7.4.1.2.2 Intensity

The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv4 Grade 5: death due to an AE.

7.4.1.2.3 Causal relationship

The assessment of the 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.

[Causal relationship to protocol-required procedure(s)]

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

7.4.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE may be documented using the categories listed below.

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

7.4.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.4.1.2.6 Outcome

The outcome of the AE may be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.4.1.3 Assessments and documentation of adverse events

7.4.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.4.1.1.

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 Ethics Committee and Regulatory Authorities.

All serious and unexpected adverse events should be reported to MD Anderson IRB and Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

The Investigator may 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 1000
Montville, NJ 07045-1000

Address:
FDX or UPS only
340 Changebridge Road
Pine Brook, NJ 07058

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone: 1-888-842-2937

7.4.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the study physician according to the applicable reference document and according to all local regulations.

7.4.1.6 **Adverse events of special safety interest:**

Since radium 223 dichloride is eliminated in the feces, but is an alpha emitter, feces containing the radiopharmaceutical can be safely disposed of by flushing down the toilet. If however there is ever an incident of placing the subjects excreta in the food of another person and the radiopharmaceutical is ingested (e.g. an alpha particle emitting special sandwich), this should be reported to the principal investigator and the principal investigator or designate should then determine whether the oral ingestion poses any safety risk (probably not) using gamma camera imaging to quantitate whether any significant bone absorption has occurred.

Long-term growth monitoring (<18 years only)

Patients with growth potential (e.g. epiphysis has significant uptake on the screening ^{99m}TcMDP scan) will have yearly growth monitored (and compared to weight and height vs weight percentile) for age until age 21 or no significant change of height is seen for 2 consecutive years- whichever is first.

Any secondary malignancies or potential long-term (i.e. > 2 months) grade 3 or greater hematologic toxicities will also be reported to MD Anderson IRB and Bayer.

Survival data will be reported yearly as long as MD Anderson Cancer Center IRB continuing review and yearly IND reporting is done. Data concerning any expected unexpected or unusual bone toxicities (e.g. hardware failure, pathologic fracture of limb salvage bones) will be collected and reported annually.

7.4.2 Pregnancies

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

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

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

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

7.4.3 Further safety

Progressive disease

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

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform MD Anderson IRB and Bayer and record the cause of death in detail (using the SAE Form) within 1 working day.

7.5 Other procedures and variables

7.6 Appropriateness of procedures / measurements

The assessments described in the previous sections are widely used and generally recognized as reliable, accurate, and relevant for determining the safety and efficacy of therapies in osteosarcoma.

8. Statistical methods and determination of sample size

8.1 Analysis sets

Safety monitoring rule

- Should DLTs occur in more than two patients at any time during the dose expansion phase clinical personnel and study investigators will meet and assess the attribution, severity and nature of the DLTs. No additional patients will be accrued until the data is reviewed and a decision is made to continue at the current dose or to de-escalate the prior dose as the dose for the expansion phase. This review and decision will be documented in writing.

Monitoring of alkaline phosphatase

- Alkaline phosphatase, a biomarker associated with osteosarcoma metastases, will be determined monthly before administration of each dose of Ra-223 dichloride. The trend of improvement (or not) will be analyzed for a particular patient and number of patients in a cohort with improvement as a function of dose # will be analyzed.

Imaging

- Nuclear Medicine Studies will use commercially available ^{99m}Tc, ^{18}Flurodeoxyglucose and sodium ^{18}Fluoride to image indicator lesions. The trend of improvement (or not) in ^{99m}Tc-MDP on SPECT CT, ^{18}FDG-PET-CT SUV, or Na^{18}F SUV will be compared for study entry vs after dose #3 and study entry vs after dose #6 and after dose #3 vs after dose #6 will analyzed for a particular patient and number of patients in a cohort with improvement after dose #3 and dose #6 will be analyzed.

- Analysis of lung metastases. Up to 3 measurable (1 cm or larger) indicator lesions seen on chest CT may be described at study entry and compared after dose #3 and dose #6. RECIST criteria (>20% increase in size) will be used as criteria for progression. Any change <20% or if size is <1 cm will not be used for “off study” progression criteria.

- RECIST progression will determine progressive disease regardless of other imaging.

8.2 Variables

Hematologic data

Alkaline phophastase (total)

Quantitative imaging data

8.3 Statistical and analytical plans: as above

8.4 Planned interim analyses: yearly at time of IND review

8.5 Determination of sample size

Dose escalation phase: 3 dose levels using standard 3+3 design (N=9)

Cohort expansion N=6

9. Data handling and quality assurance

9.1 Data recording

It is the expectation that all data has source documentation available at the site. The site must implement processes to ensure this happens.

DMI/CORe will be used as the electronic case report form for this protocol. Protocol specific data will be documented in the medical record and then entered into the case report form.

9.2 Monitoring : Data will be reviewed at each dose level, yearly when IND yearly review and IRB continuing review is submitted, and at completion of the cohort expansion

9.3 Data processing: As per Biostatistics

9.4 Audit and inspection

Inspections by regulatory health authority representatives i.e. FDA and IEC(s)/IRB(s) are possible. The investigator should notify Bayer immediately of any such inspection.

9.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

10. Premature termination of the study

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The principal investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects: IND

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to Bayer.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator 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 IEC/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 should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

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.

Since this is an investigator initiated IND study at MD Anderson, Bayer will provide a letter of to authorize the FDA to cross-reference of its current IND and well as agreement to supply Ra-223 dichloride for the purposes of this study. The MD Anderson IND Office will assist the PI and study personnel in providing yearly IND update/submissions to the FDA also.

11.2Subject information and consent

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision. Subjects <18 years old will provide written assent.

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

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's medical record

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

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

2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be

requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

11.3Publication policy

Bayer recognizes the right of the investigator to publish results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to Bayer at least thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties. All relevant aspects regarding data reporting and publication will be part of the contract between Bayer and the investigator/institution

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

11.4 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12. Reference list

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13. Amendments

13.1.1 So far none

13.1.2 Overview of Changes

13.1.3 Changes to the Protocol Text

14. Appendices- see PDOL

15. Other References- in Section 1.3.1 and can be provided by Bayer

[1]Report R-8662

[2]Report R-8663

[3]Int J Radiation Oncology 1991;21:361-367

[4]Cancer 2005;104:856-863

[5]Raabe C Health Phys 2010;98:515-536