# Title page

Phase II Trial of Ra-223 dichoride in combination with Hormonal Therapy and Denosumab in the Treatment of Patients with Hormone-Positive Breast Cancer with Bone-Dominant Metastasis

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| Test drug(s): | Ra-223 dichloride (BAY 88-8223) |
| [Study purpose:] | Defining efficacy |
| Clinical study phase: | Phase II |
| | Date: **23 January 2018** |
| Amendment no.: | 10 |
| Bayer Study no.: | **XXXXX** |
| Institution Study no.: | **2014-0508** |

Principal Investigator: Naoto T. Ueno, MD, Ph.D
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030
Phone: 713-792-8754

Co-Principal Investigator: Beth Chasen, MD

Statistician: Yu Shen Ph.D., Diane Liu, Ph.D.

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

## Synopsis

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| **Title** | Phase II Trial of Ra-223 dichoride in combination with Hormonal Therapy and Denosumab in the Treatment of Patients with Hormone-PositiveBreast Cancer with Bone-Dominant Metastasis |
| **Clinical study phase** | Phase II |
| **Study objective(s)** | Primary objective:<br>• To determine the disease control rate at 9 months in subjects with bone dominant metastatic breast cancer treated with Ra-223 dichloride + Hormonal agent + Denosumab<br>Secondary objectives<br>• To determine the tumor response rate at 6 months using PERCIST criteria.<br>• To determine the safety of Ra-223 dichloride + Hormonal agent + Denosumab.<br><br>Exploratory objectives<br>• To determine the proportion of CTCs detected by CellSearch.<br>• To determine the proportion of EMT-CTCs and investigate the correlation to CTCs by CellSearch. |

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| **Name of active ingredient**<br>**Dose(s)**<br>**Route of administration** | Ra-223 dichloride<br>55 kBq/kg body weight after implementation of NIST<br>Intravenous |
| **Indication** | |
| **Diagnosis and main criteria for inclusion** | • Pathologically or radiographically diagnosed Stage IV breast cancer with metastases to the bone and/or bone marrow.<br>• No limit in number of prior hormonal agents in metastatic breast cancer.<br>• Breast tumors with hormone receptor positive disease (ER+/PR+, ER+/PR- regardless of HER2 status).<br>• ECOG performance score of 0, 1.<br>• Age ≥ 18 years.<br>• All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.03 Grade 1 or less at the time of signing the Informed Consent Form (ICF). |
| **Study design** | <u>Study Treatment</u><br>• After signing informed consent, confirmation of eligibility, participants will receive Ra-223 dichloride + hormonal agent + denosumab.<br><u>Dosing Regimen</u><br>• Ra-223 dichloride, 55 kBq/kg will be administered as a bolus intravenous (IV) injection (up to 1 minute) through a secure in-dwelling catheter on day 1 of the study and then every four weeks thereafter for 6 cycles.<br>• A single hormonal agent (e.g., Tamoxifen or Aromatase Inhibitor or Fulvestrant) will be administered per standard FDA approved dosage.<br>• Patients will receive subcutaneous (SC) injections of denosumab 120 mg every four weeks. |
| **Type of control** | This is a single arm study. |
| **Number of subjects** | 36 |
| **Study Endpoints** | The primary endpoint is disease control rate at 9 months. |

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| **Plan for statistical analysis** | The primary endpoint is disease control rate at 9 months. With 36 patients, we will have an 85% power to detect the disease control rate of 90% against 70% with a two-sided exact binomial test at a significance level of 5%. |

**Amendment Rationale**

The quantification of radium-223 radioactivity in Xofigo® is based on the primary standardization performed by the US National Institute of Standards and Technology (NIST). The NIST Standard Reference Material is used to calibrate the instruments in production and quality control of both the drug substance and drug product. Additionally, the calibrated instruments in production at the Institute for Energy Technology (IFE, Norway) are used to prepare the NIST traceable radium-223 reference material, which are then sent to the treatment sites (e.g., nuclear medicine laboratory physicians or technicians) for dial setting of their dose calibrators, to allow verification of the patient dose. A reassessment of the primary standardization was initiated by the NIST. A discrepancy of approximately 10% between the published NIST primary standardization (Cessna, 2010, NIST 2010) and current measurements was confirmed and a revised NIST primary reference standard has been issued (Zimmerman, 2015, NIST update). As a result of the revised NIST primary standardization, an adaption of the numerical description of patient dose and the description of radioactive concentration of the drug product solution becomes necessary. This concerns Xofigo® for commercial use and product used in clinical trials.

After the implementation of the new standard (NIST update) the numerical description of the patient dose will be adjusted from 50 kBq/kg to 55 kBq/kg, and the numerical description of the radioactivity in the vial will be changed from 1,000 kBq/mL to 1,100 kBq/mL

The values in this protocol have been revised as per the United States National Institute of Standards and Technology (NIST) standardization update.

Bayer has submitted a variation application to the FDA. The current standard (NIST 2010), dial setting and dose will remain in effect until Bayer has confirmed the unique implementation date in the 2nd quarter of 2016 as agreed with FDA and notified the principal investigator Naoto T. Ueno, MD at The University of Texas MD Anderson Cancer Center.

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# List of abbreviations

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| 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-Releasing Hormone (GnRH) |
| mCi | Millicuries |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | Milliliter |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NIST | National Institutes of Standards and Technology |
| 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 particles), 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 ($^{223}Ra^{2+}$).

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

Breast Cancer Bone metastasis:

Bone is the most common metastatic site for breast cancer, and bone metastases develop in 65-75% of patients with metastatic breast cancer.[1, 2] These metastases can result in substantial morbidity in the form of skeletal-related events (SREs) that are defined as pathological fractures, spinal cord compression, hypercalcemia, or pain that requires radiation or surgery of the bone. Once bone metastases become established, they are usually incurable and the goal of treatment becomes focused on palliation and prevention of SREs.

Treatment for Breast Cancer Bone Metastasis

Modalities used to treat breast cancer that has metastasized to the bone include chemotherapy, hormonal therapy, analgesics, radiotherapy, and orthopedic surgery. Because breast cancer patients who have bone metastasis may face severe reduced quality of life due to bone-related complications, there is a need for development of bone targeting therapy for patients with hormone positive breast cancer. There is currently no bone metastasis targeted specific treatment in breast cancer. Strontium-89 and samarium-153 are FDA-approved radiopharmaceutical agents indicated for severe bone pain due to bone metastasis. But they are not indicated for a treatment of breast cancer bone metastasis.

Role of Circulating Tumor Cells in Metastatic Breast Cancer:

The FDA-approved CellSearch System (Veridex, Raritan, NJ) is the first diagnostic test to identify and enumerate circulating tumor cells (CTCs) in the bloodstream of patients with metastatic breast cancer. The analysis is based on the enumeration of epithelial cells, which are isolated from the blood by anti-EpCAM coated ferrous nanoparticles

and stained with antibodies to cytokeratin (CK) and common leukocyte antigen (CD45) and DAPI. CTCs are characterized as cells with a nucleus (DAPI+) that express surface EpCAM, cytoplasmic CK, and lack expression of CD45. CTC are an independent prognostic factor for progression-free and overall survival in metastatic breast cancer (MBC). Circulating tumor cells (CTCs) are cancer cells of epithelial origin that are found in the peripheral blood (PB) and are believed to be shed from primary lesions. In patients with MBC, the number of CTCs in the PB before and during treatment is an independent predictor of PFS and OS.[3, 4] Superior PFS and OS were observed among patients with fewer than 5 CTCs per 7.5 mL of peripheral blood regardless of primary tumor histology, hormone receptor and HER2/neu status, sites of first metastases, or whether the patient had recurrent or de novo metastatic disease. Between 10% and 30% of patients with stage I to III breast cancer and 50% to 70% of women with metastatic breast cancer have detectable CTCs.[3-5] In both cases, presence and elevation of CTCs are associated with worse prognosis. In the metastatic setting, persistent CTC after 3 to 5 weeks of a new therapy seem to indicate lack of activity of that regimen, and an ongoing prospective randomized clinical trial is addressing the relative worth of changing to an alternative treatment rather than waiting for classic clinical and radiologic evidence of progression. Early studies already suggest a role of CTCs in selected patients with metastatic disease. Coupled with an increasing understanding of the need for well-designed and well-conducted trials, better understanding of the biology of CTC will result in their becoming a routine part of the clinical evaluation of at least patients with metastatic breast and other cancers, and perhaps even in early stage disease.

Epithelial Mesenchymal Transition of CTC

In order to metastasize to distant organs, breast cancer cells must detach from the primary tumor, traverse the peripheral circulation, extravasate into the parenchyma, and establish a new tumor. A number of studies have shown that carcinoma cells often activate a transdifferentiation program, termed epithelial-mesenchymal transition (EMT), to acquire the traits needed to execute the multiple steps of metastasis. Through this EMT process, epithelial cells lose cell-cell contacts and cell polarity, downregulate epithelial-associated genes, acquire mesenchymal gene expression, and undergo major changes in their cytoskeleton. This cellular process culminates in a mesenchymal appearance and increased motility and invasiveness. Cancer cells can be induced to undergo EMT by several signaling pathways, most notably those involving the cooperation between TGF-β1 signaling and oncogenic Ras or other receptor tyrosine kinases, as well as Wnt, Notch, and the signaling activated by Hedgehog. In addition, certain transcription factors, including TWIST1, SNAIL1, SLUG, ZEB1, and FOXC2 can induce EMT in mammary epithelial cells and/or breast cancer cells. In addition, blocking the expression of Twist in the highly metastatic 4T1 murine mammary cell line reduced both metastatic burden and the number of CTCs in mice bearing xenograft

mammary tumors thus linking EMT, metastasis, and the presence of CTCs. These findings suggest that the expression of epithelial-cell surface markers, such as EpCAM, may not be optimal for detecting heterogeneous CTC population due to a subpopulation(s) with mesenchymal phenotype. We recently demonstrated that CellSearch is incapable of detecting CTC undergoing EMT (EMT-CTC) and have developed a PCR-based assay to detect EMT-inducing transcription factors (EMT-TFs) in breast cancer patients.[6]

Imaging of Bone Metastasis Ability of PET/CT to detect the tumor response

2-[Fluorine-18]fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET) is more sensitive than conventional imaging in the detection of breast cancer metastases at any site. PET has the potential to revolutionize the definition of measurable tumors because it introduces imaging criteria based on function. The regular, well-defined tumor margins that are necessary for reproducible anatomic measurements are of lesser importance in functional imaging. FDG is a radiolabeled form of glucose that cannot be metabolized and therefore accumulates in cells, which take up the molecules as if they were normal glucose. Through this accumulation, FDG activity acts as a surrogate for glucose metabolism.

Since many malignancies are highly metabolic and accumulate FDG, it is the most commonly used PET agent for oncologic indications. FDG–PET/computed tomography (CT) allows for fusion of functional and anatomic datasets, resulting in more accurate evaluation of disease, which has resulted in a better detection and reflection of the tumor activity in MBC, in particular of bone metastases. Recent prospective study, a possible correlation between>5 CTCs at baseline and the presence of bone metastases as detected by whole-body bone scan was noted. The superiority of FEG-PET/CT over bone scan in specificity and sensitivity for detection of bone metastases is well documented. So there is a possibility to detect the response of radium-223 accompanied with the reduction of CTCs in FDG-PET/CT.

The most widely used criteria are based on the anatomic measurement of solid tumors. Because bone metastases are typically located in irregularly shaped bones and are difficult to measure with rulers, they have been previously considered unmeasurable disease. New developments in cancer response criteria have increased awareness of the importance of the response of bone metastases to therapy. The recently updated Response Evaluation Criteria in Solid Tumors (RECIST 1.1) now consider bone metastases with soft tissue masses > 10 mm to be measurable disease. Response criteria specific to bone metastases have been developed at The University of Texas MD Anderson Cancer Center (MDA criteria) and can be used to assess therapeutic response in numerous types of bone metastases. Functional imaging criteria, such as the recently developed Positron Emission Tomography Response Criteria in Solid Tumors

(PERCIST) allow response to be measured in the absence of anatomic change through assessment of metabolic activity.[7-10]

As monitoring tumor response of bone metastases becomes more important in the management of cancer, so does the demand on radiologists and nuclear medicine physicians for accurate interpretation of the behavior of these lesions. The WHO criteria include radiograph-based guidelines for the interpretation of bone metastases; however, RECIST or RECIST 1.1 did not adopt these guidelines. The resultant void regarding the evaluation of bone metastases led to the development of bone-specific response criteria at MD Anderson Cancer Center in 2004.

The MDA criteria updated the UICC and WHO bone response criteria by expanding radiographic assessment and incorporating both CT and MRI. In a study comparing the MDA, UICC, and WHO criteria in 41 breast cancer patients with bone-only metastases, the MDA criteria were shown to better differentiate responders to chemotherapy from nonresponders and were the only set of criteria to correspond to progression-free survival. According to the MDA criteria, time to disease progression was 5.5 months for nonresponders and 23.3 months for responders (P = 0.025), compared with 10.4 months and 12.4 months, respectively, according to the WHO criteria (P = 0.55). The MDA criteria identified nonresponders earlier and better correlated with clinical response in the first 2-6 months of therapy than did the WHO criteria. Early signs of disease progression are valuable, allowing the halting of ineffective therapy in a timely fashion and the possible substitution of effective therapy. In addition to their utility for guiding treatment decisions, the MDA bone response criteria closely reflect the behavior of bone metastases on radiography and CT and can be used as guidelines for the interpretation of these studies whether or not a patient is enrolled in a therapeutic trial[10]

### 1.2 Rationale of the study

The objective of this protocol is to determine the progression events at 9 months by Ra-223 dichloride + hormonal agent + denosumab. Currently Ra-223 dichloride is approved by FDA only for castration resistant prostate cancer and for breast cancer the drug has been still under clinical experiments. The clinical safety of Ra-223 dichloride was evaluated in advanced breast cancer patients. [11]Its efficacy has been evaluated in castration-resistant prostate cancer patients with bone metastases in phase III multicenter study (ALSYMPCA), which demonstrated a significant survival benefit from Ra-223 dichloride. [12]

After determining its efficacy, we will plan for a definitive randomized study in SWOG. Denosumab is a FDA-approved bone modification agent. Use of denosumab and hormonal therapy for bone metastasis dominant breast cancer is considered a standard of care.

We will use progression events (the total number of events of progression among the participating patients within 9 months) instead of determining progression-free survival as the primary endpoint so that we can complete the study in a timely manner. The 9-month timeframe was chosen because our group reported that the median progression-free survival duration for patients diagnosed with hormone-positive bone-only metastatic breast cancer is 12 to 18 months and that for patients with HER-2 positive is 10 to 24 months.[1] This data suggest that there will be no progressive of disease about 70% at 9 months when bone only metastatic disease is treated with endocrine therapy alone.

We will also use FDG PET-CT scans at 6 months and 9 months to evaluate the tumor response using PERCIST criteria.[8] The assessment of the tumor response is a secondary objective.

## 1.3 Ra-223 dichloride

### 1.3.1 Mechanism of Action

Radium-223 dichloride is a therapeutic alpha particle-emitting pharmaceutical with targeted anti-tumor effect on bone metastases. 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 keV/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 is less than 100 micrometers (less than 10 cell diameters), which minimizes damage to the surrounding normal tissue.

### 1.3.2 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 Institue of Standards and Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published. The NIST SRM is used to calibrate the instrucments 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 and results obtained by other national metrology institutes (United Kingdom, Germany and Japan). After completion of the re-assessment, NIST reported their findings and had to 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 approximately + 10. 5 %. The current NIST standard for radium-223 dichloride will remain in effect until the FDA has fully approved theregulatory variation submitted for Xofigo and is anticipated in the 2nd quarter of 2016.
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.

### 1.3.3 Preclinical[13-16]

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 and started at the lowest dose of of 20 (0.00056 mCi) – 80 kBq (0.0022 mCi) per kg body weight, (22 (0.00061 mCi)-88kBq (0.0024m Ci after implementation of the NIST) with the exception of body weight decreases.

Dose-limiting myelotoxicity was seen in dogs after single administration of 450 kBq (0.012 mCi) (497 kBq/kg after implementation of NIST update) 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. The presence of neoplastic changes, other than osteosarcomas, was also reported in the longer term (12 to 15 months) rat toxicity studies. Due to its mode of action, and as seen with conventional radiotherapy and other radiotherapeutics, radium-223 dichloride may have the potential to induce secondary malignancies. 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

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 1,000 kBq (0.012 to 0.027 mCi) corresponding to 497-1100kBq ( 0.014 to 0.03 mCi) per kg body weight after implementation of the NIST (9 (dog) to 20 (rat) times the clinically recommended dose.

### 1.3.4 Clinical Experience Summary[12, 17-20]

The clinical development of Ra-223 dichloride includes phase I and phase II studies in prostate cancer patients with bone metastases. The results of these 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 50kBq (0.0012mCi) (55 kBq (0.0014 mCi)/kg after implementation of the NIST 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).

In the ALSYMPCA study, 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 first SRE (defined as time to EBRT, time to first pathological bone fracture, time to spinal cord compression and time to surgical intervention) was statistically significantly longer in the radium-223 chloride group compared to placebo (median number of months=15.6 for radium-223 chloride versus 9.8 months for placebo (HR=0.658, 95 CI 0.522–0.830, p= 0.00037).

Time to total ALP progression (defined as ≥ 25% increase compared to baseline/nadir) was statistically significantly longer in the radium-223 chloride group 7.4 months compared to placebo 3.8 months (HR = 0.167, 95% CI 0.129 – 0.217; p= <0.00001).

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 (HR = 0.643, 95% CI 0.539,0.768; p = <0.00001)

A total ALP response (defined as a confirmed ≥ 30% or ≥ 50% reduction compared to baseline) at week 12 was observed in higher proportions of subjects who were treated with radium-223 chloride group (47% and 3% respectively) compared to those in the placebo (3% and <1% respectively) group.

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. 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.

Most common hematologic adverse events all grades were anemia (31.2%), neutropenia (5%) and thrombocytopenia (11.5%). Most common non-hematologic all grades adverse events occurring in more than 15% of patients were: bone pain, diarrhea, nausea, vomiting and constipation.

Table 1 shows adverse reactions occurring in ≥ 1% of patients and for which the rate for Ra-223 dichloride exceeds the rate for placebo.

**Table 1 Adverse Reactions in the Phase III Randomized Trial[12]**

| **System/Organ Class Preferred Term** | **Ra-223 dichloride (n=600)** | | **Placebo (n=301)** | |
|---|---|---|---|---|
| | **All Grades %** | **Grades 3-4 %** | **All Grades %** | **Grades 3-4 %** |
| **Blood and lymphatic system disorders** | | | | |
| Thrombocytopenia | 11.5 | 6.3 | 5.6 | 2 |

| | | | | |
|---|---|---|---|---|
| Neutropenia | 5 | 2.2 | 1 | 0.7 |
| Leukopenia | 4.2 | 1.3 | 0.3 | 0.3 |
| Pancytopenia | 2 | 1.2 | 0 | 0 |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 25 | 1.5 (grade 3 only) | 15 | 1.7 (grade 3 only) |
| Vomiting | 18.5 | 1.7 (grade 3 only) | 13.6 | 2.3 (grade 3 only) |
| Nausea | 35.5 | 1.7 (grade 3 only) | 34.6 | 1.7 (grade 3 only) |
| **General disorders and administration site conditions** | | | | |
| Injection site reactions (including erythema, pain and swelling) | 1.2 | 0 | 0 | 0 |

Adverse reactions are identified using MedDRA version 14.1 and graded according to CTCAE version 3.0.

An additional clinically important adverse reaction observed in less than 1% of Ra-223 dichloride -treated patients and at a higher incidence than in placebo-treated patients was lymphopenia (0.8% vs. 0.3%).

**Secondary malignant neoplasms**

No cases of radiation-induced cancer have been reported in reported in clinical trials with radium-223 dichloride in follow-up of up to three years. However, the radiation dose resulting from therapeutic exposure may result in higher incidence of cancer (e.g. sarcomas of the bone, or leukemia), mutations and a potential for development of hereditary defects.

First clinical experience with alpha-emitting Ra-223 in the treatment of skeletal metastases of bone was well tolerated. Ten breast cancer patients was enrolled in a phase I trial received a single i.v. injection of Ra-223. Pain relief was reported by 52%, 60%, and 56% of the patients after 7 days, 4, and 8 weeks, respectively. 223Ra cleared rapidly from blood and was below 1% of initial level at 24 hours.[21]

## 2. Study objectives

Primary objective:

- To determine the disease control rate at 9 months in subjects with bone dominant metastatic breast cancer treated with Ra-223 dichloride + Hormonal agent + Denosumab

Secondary objectives

- To determine the tumor response rate at 6 months using PERICST criteria.
- To determine the safety of Ra-223 dichloride + Hormonal agent + Denosumab.

Exploratory objectives

- To determine the proportion of CTCs detected by CellSearch.
- To determine the proportion of EMT-CTCs and investigate the correlation to CTCs by CellSearch.

## 3. Investigators and other study participants

*Principal Investigator*

Naoto T. Ueno, MD, PhD, FACP
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030
e-mail: nueno@mdanderson.org
Phone: 713-792-8754
Fax: 888-375-2139

## 4. Study design

Study Treatment

- After signing informed consent, confirmation of eligibility, participants will receive Ra-223 dichloride + hormonal agent + denosumab.

Dosing Regimen

- Ra-223 dichloride, 50 kBq/kg ( 55kBQ/kg after implementation of the NIST) will be administered as a bolus intravenous (IV) injection (up to 1 minute) through a secure in-dwelling catheter on day 1 of the study and then every four weeks thereafter for 6 cycles.
- A single hormonal agent (eg, Tamoxifen or Inhibitor or Fulvestrant) will be administered per standard FDA approved dosage.
- Patients will receive subcutaneous (SC) injections of denosumab 120 mg every four weeks.

# 5. Study population

## 5.1 Eligibility

### 5.1.1 Inclusion criteria

- Stage IV breast cancer with metastases to the bone and/or bone marrow.
- Pathological or radiographical confirmation of metastases to the bone and/or bone marrow. The definition of radiologic diagnosis of bone metastasis is based on typical and highly reliable imaging findings in studies such as bone scan (new or multiple TC99m positive lesions), PET/CT (new or multiple FRG positive lesions), and MRI (typical T1w replacement, T2w positive and T1 plus contrast media positive) for bone metastasis with 2 or more lesions. If the bone metastasis is highly suspected or not well defined by imaging, bone biopsy is necessary for confirmation.
- Visible uptake in at least one lesion on bone scanning prior to radium therapy.
- No limit in number of prior hormonal agents in metastatic breast cancer; only one prior chemotherapy is allowed in metastatic setting. Anti-HER2 targeting therapy, CDK4/6 inhibitor, other targeted therapy (e.g., mTOR or PI3K inhibitor) in combination with hormonal treatment will be counted as one hormonal agent. Any anti-HER2 targeting therapy in combination with chemotherapy will not be counted as one additional treatment.Breast tumors with hormone receptor positive disease (ER+/PR+, ER+/PR).
- ECOG performance score of 0, 1.
- Age ≥ 18 years.
- All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v 4.03 Grade 1 or less at the time of signing the Informed Consent Form (ICF).
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 6 months 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) ≥ 3,000/mm3
    - Absolute Neutrophil Count (ANC) ≥ 1,500/mm3
    - Platelet (PLT) count ≥ 100,000/mm3
    - Hemoglobin (HGB) ≥ 10 g/dl
    - Total bilirubin level ≤ 2.0 x institutional upper limit of normal (ULN)

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN
- Creatinine ≤ 1.5 x ULN

- Subjects 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.

### 5.1.2 Exclusion criteria

- Following breast cancer disease conditions are not eligible.
  - Single Bone Lesion
  - Two or more visceral metastasis
    *Single visceral lesion < 2 cm without any laboratory changes or clinical symptoms due to the metastatic lesion is permitted.
  - Presence of brain metastases
  - Imminent spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI). *
  - Impending fracture, spinal cord compression, and/or potentially unstable compression fracture of vertebral body with possibility of cord compression.*
  - Life expectancy severely limited by concomitant illness (less than 12 months).

  *Concurrent external beam radiation therapy to non target lesion is permitted. Following prior treatments are not eligible.
  - Use of any investigational agent within 30 days preceding enrollment.
  - Treatment with cytotoxic chemotherapy within previous 4 weeks
  - Failure to achieve </= Grade 2 AE resolution from cytotoxic chemotherapy administered more than 4 weeks previous (however, ongoing neuropathy is permitted).
  - Received systemic therapy with radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188, or Ra-223 dichloride) for the treatment of bony metastases.
- Following medical conditions are not eligible.
  - Other malignancy treated within the last 3 years (except non melanoma skin cancer or low-grade superficial bladder cancer or cervical dysplasia)
  - Any other serious illness or medical condition, such as but not limited to:
  - Any 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

- Crohn's disease or ulcerative colitis
- Bone marrow dysplasia or Myelodysplastic syndrome.
- Women who are pregnant or breast-feeding. Women of childbearing potential must have a negative serum 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.
- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Major surgery within 30 days prior to start of study drug.

### 5.1.3 Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer therapy (chemotherapy, surgery, immunotherapy, biologic therapy, anti-HER 2 targeting therapies, or tumor embolization) other than Ra 223 dichloride. Concurrent external beam radiation therapy to non target lesion is permitted. Prior use of Ra-223 dichloride.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).

## 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.
- 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 and –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 except for carcinoma in situ in cervics and curatively excisable skin cancer such as basal cell carcinoma.
- 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 randomized~~;~~ assigned to treatment/run-in/wash-out 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

If patients are withdrawn before the actual start of treatment, patients will be replaced.

# 6. Treatments

## 6.1 Treatment assignment

Upon providing informed consent, the completion of all screening tests, and determination of eligibility, the participants will be assigned a treatment.

## 6.2 Ra-223 dichloride

### 6.2.1 Treatments to be administered

Ra-223 dichloride, 50kBq/Kg (55 kBq/kg after implementation of the NIST) body weight will be administered as a bolus intravenous (IV) injection (up to 1 minute) at intervals of every 4 weeks for up to 6 cycles. In addition, subject will also receive denosumab and endocrine therapy as a standard of care during the first 6 cycles of Ra-223 dichloride treatment.

### 6.2.2 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 ($^{223}RaCl_2$) 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 1000kBq/ml( 1,100 kBq/mL after implementation of NIST). 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.

Radium Ra 223 dichloride, is manufactured by Bayer Healthcare LLC will provide Ra-223 dichloride, which will be manufactured by Algeta's contract manufacturer: Institute for Energy Technology, Isotope laboratories, Kjeller, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. 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 (6.6 MBq after implementation of NIST update) at the reference day. Radium Ra-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2-8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

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.

### 6.2.3 Instructions for use / handling

#### 6.2.3.1 General warning

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 223dichloride should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

#### 6.2.3.2 Radiation protection

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

and local regulations. 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 usually be below 8 MBq (0.216 mCi) corresponding to 8.8MBq(0.238mCi) after implementation of the NIST update. 8.8 MBq (0.216 238 mCi). 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 Ra-223 dichloride and the detection of contamination with standard instruments.

### 6.2.4 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. A new reference vial will be sent to each center corresponding to the updated NIST reference material.

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) (upon notification by Bayer each center is required to update dial settings to correspond to the new NIST standard). The current dial settings are to remain in effect until Bayer obtains FULL approval from the FDA for implementation. In preparation for implementation of the NEW dial setting, the clinical study center will receive a sealed vial labeled NIST standard containing a Radium Ra-223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. The amount of Radium Ra-223 dichloride in the vial will be stated on the label. Instructions for the dial setting, including the calibration log form will be enclosed with the dispatch of the calibration sample. All sites will be notified by Bayer when FINAL regulatory approval from the FDA is in place and the updated NIST standardization is to be implemented.

### 6.2.5 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 Ra-223 dichloride considering its observed biodistribution and specific characteristics.
For an administered activity of 3.65 MBq (0.0987 Ci) 55 kBq (.0015 mCi) per kg body weight to a 73-kg adult) after implementation of the NIST, 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.

### 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. 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

After implementation of the NIST, 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 factor (DK) 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 ½ of 11.4 days. The radioactive concentration at the reference date adjusted to correspond to the new NIST standard is 1,100 kBq/mL. The volume to be administered for the current dose is calculated as follows: Body weight (kg) **X** dose (55kBq/kg body weight)/DK factor **X** 1100kBq(0.0297 mCi)/mL.
Data regarding activity should be recorded on the appropriate electronic case report form (eCRF) page.

### 6.2.8 Dose preparation

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

with the radioactive solution. 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. 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 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.

### 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 by 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 that was used in preparation and administration of the study drug, should be treated as radioactive waste and disposed in accordance with local procedure for the handling of radioactive material.

### 6.2.10 Dose Modification

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

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:

**Myelosuppression:**

Treatment-related changes in hematology parameters may occur.

• If a patient experiences CTCAE v4.03 Grade 3 or 4 neutropenia, thrombocytopenia, or anemia, the administration of study drug should be delayed until recovery to Grade 2 or better.

• If a patient experiences CTCAE v4.03 Grade 3 or 4 neutropenia, thrombocytopenia, or anemia lasting > 14 days, further study drug administrations must be discontinued.

• Blood transfusion is acceptable between study drug administrations but not prior to the start of the study. Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity.

**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 should be notified that the patient has been given radioactive drug, and should 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.

The instructions 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 in accordance with institutional requirements.

### 6.3.2 Destruction and Return

At the end of the study, unused supplies of Ra 223 dichloride 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 destruction 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-

All medication that is considered necessary for the subject's welfare, and not expected to interfere with the evaluation of the study treatment may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication).

**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 but not within 4 weeks prior to first dose of study drug.
- 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

#### 7.1.1 Tabulated overview

| Evaluation and Treatment | Screening | Cycle 1 Day 1 | Cycles 2-5 Day 1 | Cycle 6 | End of study (9 month) |
|---|---|---|---|---|---|
| **Time** | **Baseline** | **Prior to Ra-223 dichloride injection** | **Receiving Ra-223 dichloride injection** | | |
| Ra-223 dichloride IV | | X | X | X | |
| Denosumab SC every 4 weeks | X | | | | |
| Hormonal agent | *per treating physician | | | | |
| Eligibility, Screening, Consent, Registration | X | | | | |
| Medical History (prior therapies and procedures for breast cancer) | X | | | | |
| Pain Assessment | | X | | X | X |
| Physical Examinations, Vital Signs | X | | X | | X |
| ECOG Performance Status | X | X | X | X | X |
| Hematology assessment (7.1.2) | X | X | X | X | X |
| Biochemical Profiles, tumor markers* (7.1.2) | X | | | X | X |
| Serum pregnancy test | X | | | | |
| PET-CT | X | | | X | X |
| Bone scan | X | | | X | X |
| MRI (if clinically indicated) | X | | | X | X |
| Bone Marrow Aspiration and biopsy (if clinically indicated) | X | | | | X |
| CTC | X | | | X | X |
| Translational Research Studies | X | | | X | X |
| Urine NTx | X | | | X | X |
| Adverse Events | X | X | X | X | X |

After 9 months, medical history, physical examination, basic laboratory test, PET-CT and bone scan will be done every 3-6 months as part of the standard of care.

Patients will be clinically screened for adequate calcium and vitamin D supplementation. If no contraindication, calcium and vitamin D will be provided using standard of care guideline.

Adverse reactions are identified using MedDRA version 14.1 and graded according to CTCAE version 4.03.

### 7.1.2 Timing of assessments

Hematology assessments

Hematology assessment will include a complete blood count with differential, and chemistry (bilirubin, creatinine, ALT, AST, BUN, serum creatinine, sodium, magnesium, potassium, albumin, total bilirubin, and alkaline phosphatase, chloride, bicarbonate, total protein, glucose, calcium, and phosphrus.

Biochemical profiles and tumor markers
CEA and CA15.3 are to be performed at the time points indicated in sections 7.1.1.

Urine N-telopeptide (NTX)
Urine NTx is to be performed at the time points indicated in sections 7.1.1.

MRI

If spinal cord compression is clinically suspected or PET-CT cannot determine the existence of the bone metastases, patients will require an MRI of the spine. If MRI could only detect the bone metastases, MRI will be used to monitor the response at 6 and 9 months.

Bone marrow aspiration and biopsy
If bone marrow involvement by breast cancer is suspected or radiographical diagnosis of bone metastases is not reliable, bone marrow aspiration and biopsy should be performed. (See the details in section 5.1.1 Inclusion criteria) If the bone marrow involvement by breast cancer is detected then, the patient will require to be tested for the bone marrow aspiration and biopsy at 6 and 9 months.

CTC
7.5ml Peripheral blood at baseline, cycle 6 and end of study will be collected in CellSave collection tubes for enumeration of CTC by CellSearch.

Translational research studies:
5.0 ml of peripheral blood at baseline, cycle 6 and end of study will be collected in AdnaCollect tubes for the detection of CTCs using AdnaTest, a PCR-based assay that measures the expression of CTC-related gene transcripts, EpCAM, MUC1, and Her2 in EpCAM-enriched cells.

EMT-CTC
10.0 ml of peripheral blood at baseline, cycle 6 and end of study will be collected in EDTA for the detection of EMT-CTC in peripheral blood mononuclear cells

sequentially depleted of CD326+ epithelial cells and leukocytes (CD45+) and then assessed for the presence of EMT-TFs by qRT-PCR.

### 7.1.3 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 0.1.

### 7.1.4 Efficacy

All subjects who receive at least one dose of study treatment will be valid for the efficacy analysis. Efficacy evaluation will be done by bone scan and PET-CT. This trial will use the PERCIST criteria for assessment of efficacy in both primary and secondary endpoints.[8] The disease control rate at 9 months will be recorded as primary endpoint and the duration until progression and tumor response rate at 6 months as secondary efficacy endpoint.

### 7.1.5 Radiographical Methodology

PET-CT will be used to assess the treatment efficacy. PERCIST criteria will be used for efficacy evaluation for the patients with bone-metastasis only. If new lesions are detected, the disease will be defined as progression according to RECIST 1.1. Patients who require radiotherapy for a bone metastasis should be scored as a disease progression.

The PERCIST measurements will be performed by Dr. Beth Chasen.

**Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST)[8]**

| Response Category | Criteria |
|---|---|
| Complete metabolic response | Normalization of all lesions (target and nontarget) to SUL less than mean liver SUL and equal to normal surrounding tissue SUL |
| | Verification with follow-up study in 1 month if anatomic criteria indicate progression |

| | |
|---|---|
| Partial metabolic response | >30% decrease in SUL peak; minimum 0.8 unit decrease* |
| | Verification with follow-up study if anatomic criteria indicate disease progression |
| Progressive metabolic response | >30% increase in SUL peak; minimum 0.8 unit increase in SUL peak* |
| | >75% increase in TLG of most active lesion or lesions (up to 5 lesions maximum) |
| | Visible increase in extent of FDG uptake |
| | New lesions |
| | Verification with follow-up study if anatomic criteria indicate complete of partial response |
| Stable metabolic response | Does not meet other criteria |
| *Primary outcome determine is measured on the single most active lesion on each scan (not necessarily the same lesion). Secondary outcome determination is the summed activity of up to 5 most lesions (no less than 2 lesions )<br>Table modified from Wahl et al. [22] | |

## 7.2 Safety

The sponsor is responsible to comply with the local regulation and legislation for adverse events reporting.

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.

All AEs whether considered drug-related or not, will be reported with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

This trial will use the NCI-CTCAE v4.03 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

Safety variables may include but not limited to the following: laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG and, in some instances, changes in chest x-ray images, as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

### 7.2.1 Adverse events

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. The IB will be updated if any new relevant safety data are obtained.

Therapeutic monitoring should be performed following dose selection of Ra 223 dichloride in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.

All concomitant medications must be recorded in the subject's source documentation.

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.

### 7.2.1.1 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.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. IF CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, correspondent to grades 1-4. The PI or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the study. PDMS/CORe will be used as the electronic case report form for this protocol.

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. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

**Definition of serious adverse event (SAE)**

It is the responsibility of the PI and the research teams 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.

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.

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).

a. 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 INDIND Sponsor, IND Office.

b. 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 "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting 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).

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

#### 7.2.1.2 Classifications for adverse event assessment

##### 7.2.1.2.1 Intensity

The intensity of the AE is classified according to the CTCAEv4.03. Grade refers to the severity (intensity) of the AE:

**CTCAEv4.03 Grade 1**: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

**CTCAEv4.03 Grade 2**: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

**CTCAEv4.03 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).

**CTCAEv4.03 Grade 4**: life-threatening consequences; urgent intervention is indicated.

**CTCAEv4.03 Grade 5**: death due to an AE.

##### 7.2.1.2.2 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”.

#### 7.2.1.2.3 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

#### 7.2.1.2.4 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

#### 7.2.1.2.5 Outcome

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

### 7.2.1.3 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 0.1.

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.

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32. When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to 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 and report SAE to Bayer.

**Requirements for Reporting of Serious Adverse Events:**
**All SAEs must be reported to Bayer within 24 hours of the Principal Investigator's awareness and must include the following minimum information:**
**1. The name and contact information of the reporter**
**2. The name of the study drug(s)**
**3. A description of the reported SAE**
**4. A patient identified by one or more of the following:**
**a. Patient initials**
**b. Patient number**
**c. Knowledge that a patient who experienced the adverse event exists**
**d. Age**
**e. Sex**
**5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.**
Additional data which would aid the review and causality assessment of the case include but are not limited to:
The date of onset
The severity
The time from administration of study drug(s) to start of the event
The duration and outcome of the event
Any possible etiology for the event
The final diagnosis or syndrome, if known

**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:**<br>**Mail only:** | Global Pharmacovigilance - USA<br>Bayer HealthCare<br>P.O. Box 915 |

Whippany, NJ 07981-0915

**Address:** 100 Bayer Blvd. Whippany, NJ 07981
**FDX or UPS only** 67 Whippany Rd. Whippany, NJ 07981 for UPS

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

**Phone:** 1-888-842-2937

#### 7.2.1.4 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 Bayer according to the applicable reference document and according to all local regulations.

### 7.2.2 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.

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.

### 7.2.3 Further safety

**Death**

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform Bayer and record the cause of death in detail (using the SAE Form) within 24 hours.

## 7.3 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 this disease.

## 8. Statistical methods and determination of sample size

This is a single-arm, open label, phase II trial to assess the ability of Ra-223 dichloride + Hormonal agent + Denosumab responsiveness in patients with Hormone-Positive Bone-Dominant Metastatic Breast Carcinoma.

The primary endpoint is disease control rate at 9 months. With 36 patients, we will have an 85% power to detect the disease control rate of 90% against 70% based on our previous report with a two-sided exact binomial test at a significance level of 5% (See section 1.2 for details).[1]
.

The severe toxicity events defined as irreversible grade 3 and any grade 4 or greater adverse events according to CTC definition will be monitored at cohorts of 5. Toxicity rate of 20% or higher will be considered unacceptable. Bayesian beta-binomial posterior probability will be evaluated in determining the toxicity stopping boundaries. The prior distribution of toxicity rate is assumed to follow a Beta (0.2, 0.8) distribution with one patient worth of information. At any time after 5 patients have completed toxicity evaluations, the trial will be stopped if the following statement is true

$$Pr[\text{toxicity rate} > 20\% \mid \text{data}] > 0.90,$$

which means that the trial will be stopped for toxicity if the posterior probability of the toxicity rate being greater than 20% is greater than 90%. The early stopping boundaries for toxicity, shown in the format of

(The number of patients with severe toxicities) / (The number of patients treated),

are ≥ 3/5, 4/10, 6/15, 7/20, 8/25, 10/30, and 11/35.

Table 1. Operating characteristics for the stopping rules for excessive toxicity monitoring

| True DLT Rate | Probability Stop Early | Mean sample size |
|---|---|---|
| 0.05 | 0.0020 | 34.95 |
| 0.10 | 0.0202 | 34.48 |
| 0.15 | 0.0828 | 33.01 |
| 0.20 | 0.2024 | 30.47 |
| 0.25 | 0.3984 | 26.22 |
| 0.30 | 0.6242 | 21.38 |
| 0.35 | 0.7868 | 17.55 |

The toxicity monitoring boundaries and the operating characteristics are provided using Multc Lean V2.1 developed by the Department of Biostatistics at UT MD Anderson Cancer Center.

By the end of study, patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as frequency distribution, mean (± s.d.) and median (range). Due to the small scale of the study, exploratory results will be summarized based on descriptive analysis.

Disease control rate will be estimated with 95% confidence interval.

Time-to-event outcomes, including progression free survival and overall survival, will be estimated using the Kaplan-Meier method.

Toxicity data will be summarized by frequency tables, which will include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

Exploratory Research Analysis

The obtained data in all patient groups will be summarized with use of descriptive statistics such as mean, standard deviation, median, and range. Any discrete measurements of markers will be analyzed by using the Chi-square test or Fisher exact test, depending on distributions.

# 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. Data collected from the study will be entered in PDMS/CORe. The Principal Investigator is responsible for assuring that the data entered into the database is complete, accurate, and that entry is performed in a timely manner.

## 9.2 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.

## 9.3 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 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

## 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.

**Publications and NIST**

Bayer recommends inclusion of the new NIST standard in abstracts/ publications submitted OR pending publication January 2016 onwards from IIRs and other non- Bayer supported abstracts/publications for consistency. Investigators may choose to add a footnote to the publication or within the body of the publication include the new NIST standard.

## 11.2 Subject Information and consent

This adhere to the following regulations:

- Section 4.8 of the ICH E6 Guideline for Good Clinical Practice.
- Health Insurance Portability and Accountability Act (HIPAA)
- See informed consent for details.

## 11.3 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.

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

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