1. Title page

A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy

Study of radium-223 dichloride versus placebo and hormonal treatment as background therapy in subjects with bone predominant HER2 negative hormone receptor positive metastatic breast cancer

Test drug:	BAY 88-8223 / Radium-223 dichloride / Xofigo®		
Study purpose:	Efficacy and Safety		
Clinical study phase:	2	Date:	13 MAY2014
Registration:	EudraCT: 2014-002113-39	Version no.:	1.0
Sponsor's study no.:	16298		
Sponsor:	**Bayer HealthCare AG, D-51368 Leverkusen, Germany**		
Sponsor's medical expert:	Paola Zaccarini, MD Medical Expert, Oncology Bayer S.p.A. V.le Certosa 210 20156 Milan, Italy +39 02 3978 3022		

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

5.3 End of study

The end of study (EOS) will occur when the number of required events is met. All subjects on treatment at that time will be allowed to complete treatment. The 30-day safety follow-up visit is required for all subjects.

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject in any site has occurred.

6. Study population

Approximately 227 subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases will be enrolled and treated.

Eligibility

Eligibility is confirmed at the end of the screening period. At that time the subject is randomized and enters the treatment period. Administration of the first radium-223 dichloride/placebo dose may occur 1 to 3 weeks after randomization. This time is required for dose ordering and shipment. Laboratory values will be verified prior to first study drug administration as per protocol. Hematological support will be provided as needed according to the protocol guidance during the treatment period.

Rescreening

Rescreening of screen failed subjects may only be allowed after discussion with the medical monitor of the sponsor and after his/her approval. Sponsor approval of rescreening must be documented. Rescreening may be considered under the following circumstances:

- Subjects who underwent screening procedures (i.e., scans and laboratory work) that expired (are outside of the 14-day window) may need the screening procedures to be repeated in order to be within the window required prior to randomization. However, rescreening is not permitted in cases in which the initial laboratory test results do not support eligibility.
- Rescreening is also permitted where the screening procedures for subject's eligibility expired due to completion of washout periods as per protocol (e.g., 4 weeks from treatment with an investigational drug), in case of expiry of investigational product that requires replacement, or for extraordinary logistical issues.

The subjects who need to repeat the screening procedures will be asked to repeat the consenting process for study participation.

6.1 Inclusion criteria

Subjects must meet the following criteria for inclusion in the study:

- Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent. A signed ICF must be appropriately obtained prior to the conduct of any study-specific procedure.

- Documentation of histological or cytological confirmation of ER+ and HER2 negative adenocarcinoma of the breast must be available. HER2 status should be determined by an accredited/Ministry of Health approved laboratory by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), or chromogenic in situ hybridization (CISH).
- Tumors (from either primary or metastatic sites) must be ER+ defined as ≥10% positive tumor nuclei in the analyzed sample. ER+/ progesterone positive (PR+), ER+/ progesterone receptor negative (PR-) subjects are eligible whereas estrogen receptor negative (ER-)/PR+ and ER-/PR- disease will not be eligible.
- Women (≥18 years of age) with metastatic breast cancer not amenable to curative treatment by surgery or radiotherapy. Women of reproductive potential and their male partners must agree to use adequate contraception during treatment and for 6 months following the completion of treatment with radium-223 dichloride/placebo.
- Documentation of menopausal status: post-menopausal or pre-menopausal subjects are eligible.

  Note: Ovarian radiation or treatment with an LH-RH agonist/antagonist is permitted for induction of ovarian suppression.

  - **Pre-menopausal subjects** as well as subjects with ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a negative pregnancy test and agree to use an adequate method of contraception as recommended by their treating physicians
  - **Post-menopausal** status is defined either by:
    - age ≥55 years and one year or more of amenorrhea,
    - age <55 years and one year or more of amenorrhea with an estradiol assay <20 pg/mL
    - bilateral oophorectomy
- Subjects with bone dominant disease (with or without metastases in soft tissue including lymph nodes) with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by CT/magnetic resonance imaging (MRI).
- Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. All disease burden must be assessed at baseline by CT or MRI of chest, pelvis, and abdomen and any additional fields as needed. A bone scan should also be done at baseline for all subjects.

  CT/MRI done as part of the standard of practice within 6 weeks of randomization and standard of care bone scans done within 6 weeks of randomization are acceptable.

  ^{18}F-sodium fluoride positron emission tomography (PET)/CT scan is acceptable as an

alternative to technetium-99m bone scintigraphy if it is the standard of care at the institution, provided the same bone imaging modality is used throughout the study.

- Subjects must have received at least one line of hormonal therapy in the metastatic setting.

  Note: A change of the hormone agent due to progression (as per the Investigator assessment) is counted as a new line of therapy. A switch of hormone therapy from one agent to another due to toxicity or other reasons (e.g., subject's preference), in absence of PD at the time of the switch, will be counted as one line although 2 different agents have been administered.

- Subjects who are eligible for further standard of care endocrine treatment with any of the following administered as in second line or greater of hormone therapy in metastatic setting:
  - SERMs such as tamoxifen and toremifene
  - NSAIs such as anastrozole and letrozole
  - Steroidal AIs such as exemestane
  - ER down-regulators such as fulvestrant

  Subjects enrolled in the current study (signature of the ICF) will start treatment with the single hormone agent after randomization either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving the single agent hormone treatment prior to study entry are not eligible. Combination hormonal treatment is not allowed.

- Subjects must have experienced no more than 2 SSEs prior to study entry defined as: EBRT for bone pain, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

  Note: For the purpose of counting prior SREs any procedure which is related to an SRE, such as orthopedic surgery to treat a pathological bone fracture should not be counted as a separate event.

- Subjects must be on therapy with bisphosphonate or denosumab and are required to have been on such therapy for at least 3 months before the start of study treatment.
- Asymptomatic or mildly symptomatic breast cancer. A worst pain score (WPS) of 0 to 1 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in the last 24 hours) will be considered asymptomatic, and a WPS of 2 to 3 will be considered mildly symptomatic. This is to be assessed once during the screening period.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
- Life expectancy ≥6 months

- Laboratory requirements:
  - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
  - Platelet count ≥100 x 10^9/L without platelet transfusion within 3 weeks prior to randomization
  - Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 6 weeks prior to randomization
  - Total bilirubin level ≤1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert's disease)
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x institutional ULN. AST and ALT values above the ULN must not be related to liver metastases
  - Creatinine ≤1.5 x ULN
  - Estimated glomerular filtration rate (GFR) ≥60 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula
  - International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN. Subjects treated with warfarin or heparin will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of INR/PTT will be required until stability is achieved (as defined by local standard of care and based on prestudy INR/PTT values)
  - Serum albumin >30 g/L
- Able to swallow oral medication

6.2 Exclusion criteria

Eligible subjects must not meet any of the exclusion criteria listed below:

- HER2-positive breast cancer (IHC=3+, positive FISH, or positive CISH); equivocal or unknown HER2 status
  Note: *Subjects with 3+ by IHC cannot be chosen regardless of their FISH/CISH status and those with positive FISH/CISH (≥2 amplifications) cannot be chosen either, regardless of the IHC findings. Subject with 2+ by IHC will not be eligible if no negative FISH/CISH is available*.
- Subjects eligible for treatment with everolimus
- Subjects with any of the following cancers:
  - Inflammatory breast cancer
  - Bilateral breast cancer or a history of 2 distinct breast cancers
- History and/or presence of visceral metastases

- Subjects who have either received chemotherapy for metastatic disease or are considered by the treating Investigator to be appropriate candidates for chemotherapy as current treatment for metastatic breast cancer are excluded. Chemotherapy administered for adjuvant/neo-adjuvant disease is acceptable provided it was administered at least 1 year prior to study entry.
- Subjects with any previous untreated or concurrent cancer that is distinct in primary site or histology from the cancer under study, except treated basal cell carcinoma or superficial bladder tumor (Ta and Tis, American Joint Committee on Cancer, 7th edition). Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before enrollment are allowed. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of ICF).
- Subjects with known or history of brain metastases or leptomeningeal disease: subjects with neurological symptoms must undergo a contrast CT scan or MRI of the brain within 28 days prior to randomization to exclude active brain metastasis. Imaging of the central nervous system is otherwise not required
- Imminent or established untreated spinal cord compression based on clinical findings and/or MRI. Following treatment of spinal cord compression, the subject may be eligible if all other eligibility criteria are fulfilled.
- Prior treatment with radium-223 dichloride
- Prior hemibody external radiotherapy. Subjects who received other types of prior external radiotherapy are allowed provided that bone marrow function is assessed and meets the protocol requirements for hemoglobin, ANC, and platelets.
- Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188
- ECOG Performance Status ≥2
- Blood transfusions or use of erythropoietin within 6 weeks prior to randomization. Platelet transfusions are not allowed within 3 weeks prior to randomization.
- Use of biologic response modifiers, such as granulocyte macrophage-colony-stimulating factor (GM-CSF) or granulocyte-colony-stimulating factor (G-CSF), within 6 weeks prior to randomization
- Treatment with an investigational drug or with any anti-cancer treatments not permitted by the protocol, within 4 weeks prior to randomization
- Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)
- Any other serious illness or medical condition such as, but not limited to:
    - Any uncontrolled infection
    - Cardiac failure New York Heart Association Class III or IV

- Crohn's disease or ulcerative colitis
- Bone marrow dysplasia

- Previous assignment to treatment in this study

All local label specific criteria for the standard of care hormonal treatment as well as denosumab and bisphosphonates apply. Subjects must be treated according to the local standard of care requirements.

6.3 Withdrawal of subjects from study

6.3.1 Withdrawal

The study will comprise the following 4 periods:

1. Screening
2. Randomization
3. Treatment period
4. Active follow-up period with or without clinic visits

Note: Study drug (radium-223 dichloride/placebo) discontinuation (i.e., discontinuation during the treatment period) does not constitute withdrawal from the study. Every effort should be made to retain subjects who discontinue the treatment period for any reason. These subjects are to be encouraged to remain on the study for follow-up of primary, secondary, and exploratory endpoints (i.e., continue in the active follow-up period with or without clinic visits).

Subjects are expected to participate in the follow-up unless they explicitly object. Withdrawal of consent should be documented in the subject's medical file. If the subject does not wish to be followed up further, she should sign the "*Declaration of Objection to the Collection of Study Data after Withdrawal of Consent" form.*

A "dropout" is defined as a subject who has been randomized and discontinues study participation prematurely for any reason.

A "screening failure" is defined as a subject who has signed informed consent and terminates the study for any reason (e.g., failure to satisfy the selection criteria) before randomization.

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

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records (consent withdrawal [due to AE or for other reason], lost to follow-up, or death).

When a subject is withdrawn from the study, i.e., is not attending follow-up visits, the EOS page in the eCRF is to be completed.