A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with exemestane and everolimus versus placebo in combination with exemestane and everolimus when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast disorders
Study type	Interventional

Summary

ID

NL-OMON44036

Source
ToetsingOnline

Brief title
BAY 88-8223/17096

Condition

- Breast disorders

Synonym
Breast cancer, metastatic HER2 negative hormone receptor positive breast cancer with bone metastases

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer

Intervention

Keyword: Bone Metastases, Breast Cancer, Radium-223

Outcome measures

Primary outcome

The primary endpoint is:

* Symptomatic skeletal event free survival (SSE-FS)

Secondary outcome

The secondary endpoints are:

* Overall survival

* Time to opiate use for cancer pain

* Time to pain progression

* Time to cytotoxic chemotherapy

* Radiological progression-free survival (rPFS)

* Safety, acute and long term, including new primary malignancies and

hematopoietic reserve for tolerability of subsequent chemotherapy

The study will also include the following exploratory endpoints:

* Time to first on-study symptomatic skeletal event (SSE)

* Time to bone alkaline phosphatase (ALP) progression

* Bone-ALP response at Week 12 and end of treatment (EOT)

* Bone-specific rPFS

* Resource utilization

* Biomarker assessments

* Time to visceral metastases onset.

Study description

Background summary

The treatment options for patients with bone predominant metastasis of breast cancer are still limited.
Radium-223 dichloride has shown significant antitumor activity in phase II and phase III trials in subjects with bone predominant metastatic CRPC and in the phase II metastatic breast cancer study.
The safety profile and tolerability for radium-223 dichloride appear to be acceptable in this study population.
This trial is blinded, randomized, and placebo controlled for radium-223 dichloride, and it is unblinded for standard-of-care exemestane and everolimus treatment that will be received by all subjects (both arms). Best supportive care will also be received by both arms.
The mode of action of the exemestane and everolimus therapy differs from that of radium 223.
The AI exemestane binds irreversibly to the active site of the enzyme aromatase, causing its inactivation, at the primary sites of estrogen synthesis which in postmenpausal women are peripheral tissues such as adipose tissue, muscle and breast tissue. Everolimus is a selective mTOR inhibitor and acts by targeting the mTOR pathway which is thought to be a driving factor for endocrine resistance in breast cancer. Radium-223 dichloride delivers alpha radiation to bone lesions of breast cancer. Based upon these individual effects, it is expected that radium-223 dichloride treatment will prolong SSE-FS compared to placebo, when administered to HER2 negative, hormone receptor positive metastatic breast cancer patients with bone metastases that receive standard-of-care treatment with exemestane and everolimus.

Study objective

The objective of this study is to assess efficacy and safety of radium 223 dichloride in combination with exemestane and everolimus in subjects with human epidermal growth factor receptor 2 (HER2) negative, hormone receptor positive breast cancer with bone metastases.

Study design

International, phase II, double-blind, randomized, placebo-controlled, parallel group study. Randomization will be stratified by:
* Geographical regions (Europe/North America [including Israel] versus Asia)
* Previous lines of hormone therapy in metastatic setting (1 versus 2 or more): for the purpose of counting the number of prior lines of hormone therapy, only a change of the hormone agent due to progression 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 progressive disease (PD) at time of switch will be counted as one line although 2 different agents have been administered.
* Prior SREs (1 versus 2): for the purpose of prior SREs stratification, any procedure which is related to a SRE, such as orthopedic surgery to treat a pathological bone fracture, should not be counted as a separate event.

Intervention

All study subjects will receive exemestane and everolimus. You will also receive one of these treatments:
- Treatment Group 1: Radium-223 dichloride administered intravenous (into a vein) once every 4 weeks.
- Treatment Group 2: saline administered intravenous (into a vein) once every 4 weeks.
Which of these treatments you will receive will be determined by lot (like the toss of a coin)

Study burden and risks

Anticipated benefits of treatment with radium-223 dichloride include prolongation of symptomatic skeletal event-free survival (SSE FS), OS and radiological progression-free survival (rPFS), delay of SSEs, palliation of bone pain, and improvement in quality of life.

The risk profile attributed to radium-223 dichloride is favorable compared with available products for the treatment of metastatic breast cancer. The anticipated risks attributed to radium-223 dichloride include the following AEs: gastrointestinal (constipation, transient but treatable diarrhea, nausea and vomiting); hematological (transient reduction in neutrophil count, mild to moderate myelosuppression, low grade thrombocytopenia). Due to its radioactive nature, radium-223 dichloride has the potential of inducting long-term

toxicities such as other primary cancers. Current ongoing studies have an increased follow-up of 7 years to asses this potential.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* 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 trial-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), chromogenic in situ hybridization (CISH) other validated in situ hybridization (ISH) assay for detection of HER2 gene expression.

* Tumors (from either primary or metastatic sites) must be ER+ defined as *10% positive tumor nuclei in the analyzed sample. ER+/progesterone receptor positive (PR+) and 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: postmenopausal subjects or pre-menopausal subjects with ovarian radiation or concomitant therapy with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist are eligible.
- pre-menopausal subjects with ovarian radiation or concomitant treatment with LH-RH agonist/antagonist must have a plasma/serum estradiol assay of <20pg/mL at screening within 7 days prior to randomization. These subjects must also have a negative pregnancy test at screening and agree to use an adequate method of contraception as recommended by their treating physician.
o Post-menopausal status is defined either by:
o age *55 years and one year or more of amenorrhea,
o age <;55 years and one year or more of amenorrhea with a plasma/serum estradiol assay <20 pg/mL
o bilateral ovariectomy
* Subjects with bone dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by CT/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle fat, lymph nodes) and/or visceral metastases is allowed.
* 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 within 3 weeks prior to randomization by CT or MRI of chest, pelvis, and abdomen and any additional fields as needed. A Tc99m bone scan should also be done within 3 weeks prior to randomization for all subjects. CT/MRI done as part of the standard of practice within 3 weeks prior to randomization and standard-of-care Tc99m bone scans done within 3 weeks prior to randomization are acceptable. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan, if performed as part of standard of care imaging, can be used as an adjunct to CT/MRI in line with RECIST 1.1 guidelines. If FDG PET/CT scan, the CT component of the scan can be used for tumor measurements only if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (See also Appendix 16.2). FDG PET/CT or NaF 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 experienced recurrent/progressive disease following treatment with a non-steroidal aromatase inhibitor (letrozole or anastrozole) in an adjuvant or metastatic setting.
* Subjects must have received at least one line of hormonal therapy in the metastatic setting.
* Subjects who are eligible, as per the Investigator*s assessment and according to the local label, for treatment with exemestane and everolimus as a second line or greater of hormone therapy in a metastatic setting. Subjects enrolled in the current study (signature of the informed consent), will start treatment with exemestane and everolimus, after

randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo.
* Subjects must have experienced no more than 2 SREs 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.
* Subjects must be on therapy with bisphosphonates or denosumab for at least 1 month before start of study treatment.
* Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1
* Life expectancy *6 months
* Laboratory requirements:
o Absolute neutrophil count *1.5 x 109/L
o Platelet count *100 x109/L without platelet transfusion within 3weeks prior to randomization
o Hemoglobin (Hb) *9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 6 weeks prior to randomization
o Total bilirubin level *1.5 x institutional upper limit of normal (ULN) (except for subjects with documented Gilbert*s disease)
o 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
o Creatinine *1.5 x ULN
o Estimated glomerular filtration rate *30 mL/min/1.73m2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula
o 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)
* Able to swallow oral medication

Exclusion criteria

* HER2-positive breast cancer (immunohistochemistry [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/ other ISH validated assay status and those with positive FISH/CISH/other ISH validated assay cannot be chosen either, regardless of the
IHC findings. Subjects with 2+ by IHC will not be eligible if no negative FISH/CISH/other ISH validated assay for detection of HER2 gene expression is available.
* Patients with immediately life-threatening visceral disease, for whom chemotherapy is the preferred treatment option.
* Lymphangitic carcinomatosis
* Patients with ascites requiring paracentesis wihtin 2 weeks prior to study entry (signature of informed consent) and during the screening period.
*Subjects with any of the following cancers:
o Inflammatory breast cancer

o Bilateral breast cancer or a history of 2 distinct breast cancers.
* History 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 Hb, absolute neutrophil count, and platelets.
* Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188.
* ECOG PS *2.
* Blood transfusions, platelet transfusions or use of erythropoietin within 4 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 or granulocyte colony stimulating factor, within 4 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:
o Any uncontrolled infection
o Cardiac failure New York Heart Association Class III or IV
o Crohn*s disease or ulcerative colitis
o Bone marrow dysplasia;* Previous assignment to treatment in this study;All local label specific criteria for exemestane and everolimus as well as standard-of-care denosumab and bisphosphonates will apply. Subjects must be treated according to the local standard-of-care requirements.
* Breast feeding women
* Known hypersensitivity to the active substance or to any of the excipients of Ra-223 dichloride, exemestane, and everolimus or to other rapamycin derivatives. All local label specific criteria for exemestane and everolimus as well as standard-of-care denosumab and

bisphosphonates will apply. Subjects must be treated according to the local standard-of-care requirements.
* Subjects who received prior treatment or are already receiving everolimus treatment prior to study entry are not eligible.
* Known presence of osteonecrosis of jaw.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-06-2015
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Everolimus
Generic name:	Everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Exemestane
Generic name:	Exemestane
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Xofigo
Generic name:	Radium-223 Dichloride

Ethics review

Approved WMO Date:	01-12-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002114-23-NL
CCMO	NL50962.056.14