Document Type:	Clinical Study Protocol
Official Title:	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
NCT Number:	NCT02258451
Document Date:	04 Dec 2019

Cover page of the integrated clinical study protocol

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

For this study, the protocol and subsequent protocol amendment were released as follows:

- Original protocol, Version 1.0, dated 06 MAY 2014
- Amendment 1 (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 16 MAR 2015
- Amendment 2 (local amendment, France only) dated 29 APR 2015
- Amendment 3 (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 29 JUL 2015
- Amendment 4 (local amendment Italy only) 25 JUL 2015
- Amendment 5 (global amendment described in Section 15.3) forming integrated protocol Version 4.0, dated 09 MAR 2016
- Amendment 6 (local amendment Japan only) dated 13 SEP 2016
- Amendment 7 (local amendment France only) dated 31 OCT 2016
- Amendment 8 (global amendment described in Section 15.4) forming integrated protocol Version 5.0, dated 23 MAY 2017
- Amendment 9 (global amendment described in Section 15.5) forming integrated protocol Version 6.0, dated 03 APR 2018
- Amendment 10 (global amendment described in Section 15.6) forming integrated protocol Version 7.0, dated 04 DEC 2019

This document integrates the original protocol and all global amendments.

1. Title page

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

Study of radium-223 dichloride in combination with exemestane and everolimus versus placebo in combination with exemestane and everolimus 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:	04 DEC 2019
Registration:	EudraCT: 2014-002114-23	Version no.:	7.0
Sponsor's study no.:	17096		
Sponsor:	**Bayer AG, D-51368 Leverkusen, Germany** US territory: Bayer Healthcare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915 Whippany NJ 07981-0915 USA		
Sponsor's medical expert:	PPD 100 Bayer Boulevard | PPD Whippany, NJ 07981-0915, US Phone: PPD		

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: PPD

Date: 11 Dec 2019 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's Investigator site file.

2. Synopsis

Title	**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**
Short title	Study of radium-223 dichloride in combination with exemestane and everolimus versus placebo in combination with exemestane and everolimus in subjects with bone predominant HER2 negative hormone receptor positive metastatic breast cancer
Clinical study phase	Phase 2
Study objectives	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. The **primary endpoint** is: 1. Symptomatic skeletal event-free survival (SSE-FS) The **secondary endpoints** are: 2. Overall survival 3. Time to opiate use for cancer pain 4. Time to pain progression (only in subjects with baseline worst pain score (WPS) ≤8) 5. Time to cytotoxic chemotherapy 6. Radiological progression-free survival (rPFS) 7. Pain improvement rate 8. 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**: 9. Time to first on-study symptomatic skeletal event (SSE) 10. Time to bone alkaline phosphatase (ALP) progression 11. Bone ALP response at Week 12 and 4 weeks (± 7 days) after last radium-223 dichloride/placebo dose 12. Bone-specific rPFS 13. Resource utilization

	14. Biomarker assessments 15. Time to visceral metastases onset (in subjects with no visceral disease at baseline) *Safety endpoints were reported/measured as AEs. Acute safety was documented as the incidence of TEAEs. Long-term safety was documented as the incidence of post-treatment AEs. Hematopoietic reserve for tolerability of subsequent chemotherapy was assessed via the incidence of treatment emergent hematological toxicity and the incidence of post-treatment chemotherapy-related AEs. **Note:** After implementation of **CSP Amendment 9,** subjects who completed the EOT visit could be transferred to a separate extended safety follow-up study for their remaining follow-up. After implementation of **CSP Amendment 10**, all such subjects will be transferred; only subjects on oral treatment will remain on study, and no post-treatment data will be collected beyond the 30-day safety follow-up (EOT visit). As the key efficacy objectives will have been accomplished, long-term safety transferred, and only a limited number of subjects will remain in this study, in order to reduce the burden to study subjects, collection of data will be reduced and will focus mainly on **acute safety, SSE, and OS**. Once subjects are rolled over, the long-term safety will be collected and assessed entirely in the separate extended safety follow-up study
Test drug	BAY 88-8223
Name of active ingredient	Radium-223 dichloride
Dose	50 KiloBecquerel (kBq)/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight every 4 weeks for 6 cycles
Route of administration	Intravenous (IV) injection (slow bolus)
Duration of treatment	6 cycles at 4-week intervals (24 weeks)
Reference drug	Matching placebo (normal saline)
Name of active ingredient	Not applicable
Study treatment	All study subjects will receive study treatment with exemestane and everolimus, and best supportive care

Indication	Subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases treated with radium-223 dichloride in combination with exemestane and everolimus
Diagnosis and main criteria for inclusion and exclusion	Subjects must meet the following criteria for inclusion in the study: 1. Have provided written informed consent. Subjects must be able to understand and be willing to sign the written informed consent. A signed informed consent form (ICF) must be appropriately obtained prior to the conduct of any trial-specific procedure. 2. Documentation of histological or cytological confirmation of estrogen receptor positive (ER+) and HER2 negative adenocarcinoma of the breast must be available. Human epidermal growth factor receptor 2 status should be determined by an accredited/Ministry of Health approved laboratory by immunohistochemistry, fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) or other validated in situ hybridization (ISH) assay for detection of HER2 gene expression. 3. Tumors (from either primary or metastatic sites) must be ER+ defined as ≥10% positive tumor nuclei in the analyzed sample. Estrogen receptor positive/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. 4. 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. 5. Documentation of menopausal status: postmenopausal subjects or premenopausal subjects with ovarian radiation or concomitant therapy with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist are eligible. o **Premenopausal** subjects with ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a plasma/serum estradiol assay within local laboratory postmenopausal range at screening, performed 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

physicians.

- **Postmenopausal** 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 a plasma/serum estradiol assay within local laboratory postmenopausal range, performed within 7 days of randomization,
  - bilateral ovariectomy.

6. Subjects with bone-dominant disease with at least 2 skeletal metastases identified at baseline by bone scintigraphy and confirmed by computed tomography (CT)/magnetic resonance imaging (MRI). Presence of metastases in soft tissue (skin, subcutaneous, muscle fat, lymph nodes) and/or visceral metastases is allowed.
7. Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors v1.1 criteria. All disease burdens 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 technetium-99m 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 technetium-99m 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 Response Evaluation Criteria in Solid Tumors 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.
8. Subjects must have experienced recurrent/progressive disease following treatment with a non-steroidal aromatase inhibitor (letrozole or anastrozole) in an adjuvant or metastatic setting.
9. 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 progressive disease at time of switch, will be counted as one line although 2 different agents have been administered. 10. 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 therapy in a metastatic setting. Subjects enrolled in the current study will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. 11. Subjects must have experienced no more than 2 skeletal-related events (SREs) prior to study entry defined as: Need for external beam radiotherapy (EBRT) to bone, pathological bone fracture (excluding major trauma), spinal cord compression and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted. *Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization. Separate SRE events are the ones that occur at least 21 days apart from each other to ensure that linked events (eg, surgery to repair a fracture or multiple doses of radiation during a course of treatment) are not counted as separate events. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions for the different anatomical locations, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.* 12. Subjects must be on therapy with bisphosphonates or denosumab for at least 1 month before start of study treatment. 13. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1. 14. Life expectancy ≥6 months. 15. Laboratory requirements: o Absolute neutrophil count ≥1.5 x 10^9/L o Platelet count ≥100 x10^9/L without platelet transfusion within 4 weeks prior to randomization o Hemoglobin (Hb) ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 weeks prior to randomization o Total bilirubin ≤1.5 x institutional upper limit of

normal (ULN) (except for subjects with documented Gilbert's disease)
- Aspartate aminotransferase and alanine aminotransferase ≤2.5 x institutional ULN
- Pulse oximetry O_2 saturation >92% if lung metastases are present
- Creatinine ≤1.5 x ULN
- Estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease abbreviated formula. (Note: please refer to local labeling for administration of full dose of bisphosphonates)
- International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban or aspirin (e.g. ≤100 mg daily) 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 for anticoagulants that require their monitoring as per local label.
- Serum albumin >30 g/L

16. Able to swallow oral medication.

Exclusion criteria

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

1. 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.
2. Patients with immediately life-threatening visceral disease, for whom chemotherapy is the preferred treatment option
3. Lymphangitic carcinomatosis
4. Patients with ascites requiring paracentesis within 2 weeks prior to study entry (signature of informed consent) and

	during the screening period 5. Subjects with inflammatory breast cancer 6. 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. 7. 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). 8. 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. 9. 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. 10. Prior treatment with radium-223 dichloride. 11. 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. 12. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188. 13. ECOG PS ≥2. 14. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior to randomization. 15. Use of biologic response modifiers, such as granulocyte macrophage colony-stimulating factor or granulocyte colony-stimulating factor, within 4 weeks prior to randomization. 16. Treatment with an investigational drug or with any anti-

	cancer treatments not permitted by the protocol, within 4 weeks prior to randomization 17. Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone) 18. 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 19. Previous assignment to treatment in this study 20. Breast-feeding women 21. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride, exemestane, and everolimus or to other rapamycin derivatives 22. Subjects who received prior treatment or are already receiving everolimus treatment prior to study entry are not eligible 23. Known presence of osteonecrosis of jaw 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.
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 at time of switch will be counted as one line although 2 different agents have been administered. • Visceral disease yes versus no

Methodology	Prior to the primary analysis, the study comprised 4 periods: screening, randomization, treatment, and the follow-up period (active follow-up with clinic visits and active follow-up without clinic visits). **Screening period:** All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the ICF. The screening period will consist of multiple evaluations that will take place within 3 weeks prior to randomization to ensure that all eligibility criteria are met. **Randomization:** After all screening assessments have been completed and the subject's eligibility has been confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with radium-223 dichloride (Arm A - investigational arm) or placebo (Arm B - control arm). All subjects receive open-label study treatment exemestane and everolimus and supportive care according to the local standard of practice. **Treatment period:** The total treatment period is defined from the day of randomization until 4 weeks after the last administration of study treatment (radium-223 dichloride/placebo and exemestane and everolimus whichever occurs last). The study treatment consists of up to 6 cycles of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight (Arm A) or placebo (Arm B) each separated by an interval of 4 weeks ±7 days, in combination with exemestane and everolimus followed by ongoing treatment for all subjects with exemestane and everolimus as applicable. Subjects enrolled in the current study, will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving exemestane and everolimus prior to study entry are not eligible. **After Primary Analysis** (after implementation of Amendment 10): Following the administrative data review (per Amendment 8) conducted on DEC 2017 by a small group of unblinded Sponsor employees, independent of the study team, subject enrollment in this trial was discontinued on APR 2018. Following primary analysis cutoff, treatment with exemestane and everolimus will continue until disease progression, initiation of new anti-cancer therapy, unacceptable toxicity occurs, discontinuation of study treatment for other reasons, or study is terminated, whichever occurs first. All subjects will receive supportive care, as per local

	standard of practice. Assessments following primary analysis will mainly focus on acute safety, SSE and OS, as described below. At the time Amendment 10 is implemented, all subjects completed or discontinued radium-223 dichloride/placebo treatment. During the treatment period, subjects will be assessed for safety at each treatment visit, every 8 weeks. Subjects will be assessed for radiologic progression according to local standard practice. • All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AE(s) or SAEs, if the criteria of SAE were met, regardless of the Investigator's causality assessment. • All occurrences of any additional malignancies, including AML, and hematological conditions such as MDS, aplastic anemia, or myelofibrosis must be reported as SAEs, regardless of the Investigator's causality assessment. • Subjects who experience disease progression during the protocol defined treatment period, initiate new anti-cancer therapy, experience unacceptable toxicity or discontinue the study treatment for other reasons, at the end of the treatment period, will be transferred to the separate extended safety follow-up study (BAY 88-8223 study 16996 / NCT02312960). All ongoing subjects at the time of study termination will finish all study treatments as part of the study. **Follow-up period:** Following primary analysis, active follow-up in this study will be discontinued. Follow-up will be conducted in the separate extended safety follow-up study (please refer to the applicable section below). **Long-term follow-up in the separate extended safety follow-up study:** All subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, will be transitioned into a separate extended safety follow-up study (BAY 88-8223 study 16996 / NCT02312960). The separate extended safety follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The primary objective of this study is to define the long-term safety profile of radium-223 dichloride. All subjects who transition into this separate extended safety follow-up study will require a separate signed informed consent. All efforts will be made to transition all subjects to the extended safety follow-up study.

	This study will end at the time the last subject on treatment discontinues oral exemestane and/or everolimus treatment and completes end of treatment visit or discontinues from this study for another reason (e.g., death, consent withdrawn and active objection for further data collection). Until the transition to the extended safety follow-up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.
Type of control	Placebo-control arm
Number of subjects	311 subjects in total (with 1:1 randomization)
Primary variable	Symptomatic skeletal event-free survival
Time point/frame of measurement for primary variable(s)	The primary variable/endpoint, SSE-FS, is defined as the time from randomization to the occurrence of one of the following: (1) An on-study SSE, which is defined as: a. the use of EBRT to relieve skeletal symptoms b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) c. the occurrence of spinal cord compression d. a tumor related orthopedic surgical intervention. (2) Death from any cause *Note:* All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.
Plan for statistical analysis	The analysis of efficacy will be performed using the intent-to-treat population, defined as all subjects who are randomized. The primary efficacy analysis of SSE-FS will be performed using a log-rank test, stratified by the same factors as the randomization factors (i.e., geographic region, prior lines of hormone therapy in metastatic setting, and visceral disease). A one-sided alpha of 0.1 will be used for the analysis of SSE-FS. Assuming a one-sided alpha of 0.1, power of 90%, the median SSE-FS for the control group is 8.3 months and a randomization ratio of 1:1 between treatments, approximately 160 events will be required to detect a 50% increase in SSE-FS for a total of 311 subjects in the 2 treatment groups combined. The secondary time-to-event efficacy endpoints will be analyzed using a log-rank test, stratified by the same factors as the randomization factors. The exploratory time-to-event efficacy endpoints will be analyzed using a log-rank test, stratified by the same factors as the randomization factors.

	The analysis of safety will be descriptive only (no statistical test will be applied). Following primary analysis, at the closure of the study, after the last subject has discontinued treatment and study assessments, an updated analysis will be performed. The updated analysis will be descriptive only and may consist of listings.

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List of abbreviations

AE	Adverse event
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
ALT	Alanine aminotransferase
AML	Acute myelocytic leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCE	Bone collagen equivalents
BPI-SF	Brief Pain Index-Short Form
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CISH	Chromogenic in situ hybridization
Cl	Chloride
CR	Complete response
CRO	Contract Research Organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events; version 4.03
DK	Decay correction factor
EBRT	External beam radiotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
ER	Estrogen receptor
ER-	Estrogen receptor negative
ER+	Estrogen receptor positive
EU	European Union
FDA	United States Food and Drug Administration
FDG	F-18 fluorodeoxyglucose
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
IBW	Ideal body weight
ICF	Informed consent form
ICSR	Individual case safety reports

ICTP	I collagen telopeptide
IDRC	Independent Data Review Committee
IEC	Independent Ethics Committee
IHC	ImmunoHistoChemistry
IMP	Investigational medicinal product
INR	International normalized ratio of prothrombin time
IPM	Increase in pain management
IRB	Institutional Review Board
ISH	In situ hybridization
ITT	Intent-to-treat
IUD	Intra-uterine device
IV	Intravenous
IXRS	Interactive Voice/Web Response System
K	Potassium
kBq	KiloBecquerel; SI unit of radioactivity
kg	Kilogram
LDH	Lactate dehydrogenase
LH-RH	Luteinizing hormone-releasing hormone
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndromes
mL	Milliliter
mRECIST 1.1	Modified Response Evaluation Criteria in Solid Tumors version 1.1
MRI	Magnetic resonance imaging
Na	Sodium
NCI	National Cancer Institute
NIST	National Institute of Standards and Technology
NSAI	Non-steroidal aromatase inhibitor
NTX	N-terminal telopeptide (a bone biomarker for collagen crosslinking)
OS	Overall survival
PD	Progressive disease/pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PRD	Patient ready dose
PR	Progesterone receptor
PR-	Progesterone receptor negative
PR+	Progesterone receptor positive
PS	Performance status
PSA	Prostate specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
RANKL	Receptor activator of NF–κB ligand
RAVE	Medidata Rave; electronic data capture tool
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SERM	Selective estrogen receptors modulator

SPECT	Single photon emission tomography
SRE	Skeletal-related event
SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event – free survival
SUSAR	Suspected unexpected serious adverse reaction
TBW	Total body weight
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WPS	Worst pain score

Definitions of terms

Radium-223 dichloride The investigational product, a targeted alpha particle emitting radiopharmaceutical, is a ready-to-use solution for intravenous injection containing the drug substance radium-223 dichloride. The active moiety is the alpha particle emitting nuclide radium-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 radium-223 administered.

3. Introduction

3.1 Metastatic breast cancer

Breast cancer is by far, the most common cancer among women worldwide with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). It is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total) and the second cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer.(1)

Despite recent progress in diagnostic and therapeutic approaches of early breast cancer, a significant proportion of patients relapse following adjuvant treatment and approximately 5% to 6% of women present with metastatic disease at the time of their initial diagnosis.

The clinical presentation in the metastatic setting may range from an aggressive clinical course in patients with multiple and/or extensive organ involvement, to a rather indolent clinical course in those with a solitary or only few metastatic lesions (oligometastatic disease).

Depending on the extent of metastatic involvement, the prognosis is variable ranging from a median overall survival (OS) time of 26 months in patients with bone metastases only, to 21 months in patients with bone and visceral metastases, and 18 months in patients with visceral metastases only.(2)

Patients with metastatic disease are unlikely to be cured with actual available therapies. As cure is unlikely in the metastatic setting, prolongation of survival, disease control, improvement/maintenance of quality of life and palliation of cancer-related symptoms are reasonable goals of therapy.

Various therapeutic approaches are available; however, there are few widely accepted standards. Most patients will receive systemic therapies such as chemotherapy, endocrine therapy, biologic/targeted molecular therapies, bone-targeted agents as well as supportive care. The selection of a certain type of therapy over the other depends upon factors such as, tumor/disease characteristics (hormone receptor status, human epidermal growth factor receptor 2 [HER2] status, extent of metastatic involvement, disease clinical behavior, etc.), prior therapies and disease response to prior therapies, patient characteristics (i.e., comorbidities and estimated treatment tolerability, menopausal status), availability and costs of therapeutic agents and, last but not least, patient preference.

Participation in well-designed clinical trials should always be considered in patients with metastatic breast cancer.

Patients with rapidly progressing or symptomatic or visceral disease as well as those patients with hormone receptor–negative tumors or with disease that is resistant to hormonal therapy are candidates for chemotherapy.

Patients with HER2/neu positive disease are candidates for anti-HER2-targeted agents (i.e., herceptin, lapatinib).

3.2 HER2 negative and hormone receptor-positive metastatic breast cancer

Presence of estrogen receptor (ER) and/or progesterone receptor (PR) is one of the most important prognostic/predictive factors in breast cancers. Approximately 70% to 75% of patients with invasive breast cancer have hormone receptor (ER and/or PR) positive disease at the time of diagnosis.(3)

Patients with hormone receptor positive disease and HER2-negative disease are candidates for endocrine therapy unless one of the factors described above would prompt the selection of another type of therapy (i.e., chemotherapy in a patient with an aggressive clinical course and rapid pace of progression). Endocrine therapy will very likely have a beneficial effect in these patients and fewer side effects in comparison with chemotherapy.(4,5)

Selection of the first-line endocrine agent is generally based on the menopausal status, type of endocrine agent in the adjuvant setting, timing of relapse following treatment in the adjuvant setting and tolerability. First-line endocrine therapy is usually continued until the patient experiences disease progression or unacceptable toxicity.

Additional lines of therapy may include another endocrine agent (not previously administered) or another type of therapy such as cytotoxic therapy. There are no widely accepted standards/definitive recommendations for a specific treatment sequence, number of lines of endocrine therapy, and the therapeutic decision should be again based on the factors described above.

Endocrine therapy exerts its action either by reducing estrogen production or by interacting with ERs.

Various endocrine agents are currently in use:

- Selective estrogen receptor modulators (SERM): Tamoxifen and toremifene. SERMs act by antagonizing the action of estrogen in breast tissue. At the same time they also mimic the action of estrogen in other tissues, such as bone and endometrium.(6)
- Third generation aromatase inhibitors (AIs) block peripheral estrogen synthesis by inhibiting aromatase, the enzyme responsible for the peripheral conversion of androgens to estrogen.(7) Currently available third generation aromatic inhibitors (AIs) are the non-steroidal AIs (NSAI) anastrazole and letrozole and the steroidal AI, exemestane. In the first-line setting, large phase III trials have shown that all 3, anastrozole, letrozole and exemestane are equivalent or superior to tamoxifen in women with metastatic disease.(8,9,10,11)
- Estrogen receptor down regulators: Fulvestrant is a competitive ER antagonist. It blocks the actions of estrogens at the level of the receptor without any known partial agonist (estrogen-like) activity. Fulvestrant has been approved by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following prior anti-estrogen therapy based on results of published clinical studies.(12,13,14)
- Luteinizing hormone-releasing hormone analogues: Goserelin, leuprorelin, triptorelin.
- Other: estrogens, progestins, anabolic steroids

Recently published data from a phase II study shows that addition of everolimus to tamoxifen in hormone receptor positive HER2 negative patients who progressed on prior AI treatment significantly improved the clinical benefit rate, time to progression (TTP).(15)

In addition to this, data from the phase III BOLERO-2 study showed that the addition of everolimus to exemestane significantly improved progression-free survival (PFS) compared with single-agent exemestane in estrogen receptor positive (ER+), HER2-negative patients whose metastatic disease was refractory to prior treatment with letrozole or anastrozole.(16) This led to the recent marketing approval of everolimus by the FDA and EMA for the

treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a NSAI.

At the time of final analysis with a median follow-up of 18 months, the median PFS (as per Investigator review) was 7.8 months for everolimus and exemestane versus 3.2 months for placebo and exemestane (hazard ratio [HR] = 0.45, 95% confidence interval [CI]: 0.38 to 0.54; log-rank p<0.0001).(17)

Subgroup analyses also indicate that the effect of everolimus in addition to exemestane was consistent across patient subgroups and substantially prolonged median PFS regardless of prior therapies or baseline disease characteristics such as presence of visceral disease or skeletal involvement. In patients with bone-only metastases at the time of study entry (21% of total study population), the median PFS was 12.88 months in the everolimus plus exemestane group versus 5.29 months in patients on exemestane only (HR = 0.33). Patients with visceral metastases had a worse outcome, however, the improvement in median PFS was significant with median PFS of 6.83 months for everolimus plus exemestane group versus 2.76 months for placebo plus exemestane group (HR = 0.47).

3.2.1 Bone metastasis in HER2-negative and hormone receptor-positive metastatic breast cancer

Bone is a frequent site of metastatic spread with approximately 65% to 75% of patients with metastatic breast cancer having skeletal involvement.(18) The skeleton is the first site of distant spread in 46% to 47% of patients with breast cancer. The presence of skeletal metastases correlates significantly with estrogen and progesterone receptor positivity.(19,20) Bone-only metastases have been reported to occur in 17% to 37% of women with metastatic breast cancer.(21,22,23)

Results of a recent meta-analysis from 41 randomized trials that compared bisphosphonates to no bisphosphonates and including data from 17,751 breast cancer patients, suggests that adjuvant bisphosphonates reduce bone recurrences and improve breast cancer survival in postmenopausal women. Reductions in bone recurrence for postmenopausal women were similar independent of ER status, nodal involvement, bisphosphonate type, treatment schedule, or use of concomitant chemotherapy.(24)

Prognosis of patients with metastases confined to bone-only seems to be better compared to patients with visceral involvement with median survival times from the diagnosis of metastatic disease to death between 24 to 36 months as reported per different publications.(2,22,23,25,26) Occurrence of osseous metastases interferes with normal bone homeostasis and impacts the normal remodeling process by disrupting the fine balance between new bone formation and bone resorption processes. This finally results in loss of bone integrity and loss of function.

The most common sites of bone involvement are axial bones, however, other locations may also be encountered although with a lower frequency. Bone lesions may be of osteolytic, osteoblastic or mixed phenotype as per the radiographic appearance of the lesions. It is well known that bone metastases from breast cancer usually show osteolytic changes. However, interestingly, as per a retrospective study, when comparing the morphology of breast cancer bone metastases by computed tomography (CT) in the time period 1996 to 2000 versus 2001 to 2005, a higher prevalence of osteoblastic metastases was observed in the later period (1996 to 2000: osteolytic 53.7%, osteosclerotic 32.1%, mixed type 14.3%; 2001 to 2005: osteolytic

9.4%, osteosclerotic 71.9%, mixed type 18.7%). This might be due to the application of systematic bisphosphonate treatment.(28)

Due to the disrupted bone remodeling process, patients with metastatic bone lesions are at risk of increased morbidity including skeletal-related events (SREs) such as bone pain requiring intervention (i.e., radiotherapy or surgery), pathologic fractures, spinal cord compression, as well as symptomatic hypercalcemia and bone marrow infiltration. These events will ultimately impair patient's quality of life and functional independence.

A multidisciplinary therapeutic approach is generally recommended in patients presenting with bone metastases. Current therapeutic options include systemic therapies such as endocrine therapies, chemotherapy, and bone-targeted agents (i.e., bisphosphonates, denosumab). Local therapies such as external beam radiotherapy (EBRT) as well as other supportive interventions (i.e., orthopedic interventions for prevention/correction of pathological fractures) are also an important part of the therapeutic management for symptom palliation.

Use of systemic bone-targeted agents such bisphosphonates as well as the newer anti-receptor activator of nuclear factor Kappa-B ligand (RANKL) antibody, denosumab demonstrated a beneficial effect in patients with metastatic bone disease. While bisphosphonates inhibit osteoclast-mediated bone resorption, denosumab, a monoclonal antibody, inhibits key pathways in the vicious cycle of bone metastases by binding to RANKL, a mediator that stimulates increased osteoclast activity.

Several clinical trials have demonstrated the efficacy of bisphosphonates in women with bone metastases from breast cancer.(29,30,31,32)

More recently, denosumab has been found to be more effective than zoledronic acid as measured by the time to first and subsequent on-study SREs in patients with bone metastases.(33,34) The median time to the first on-study SRE was 26.4 months for zoledronic acid and was not yet reached for denosumab at time of reporting. Denosumab was approved for the treatment of patients with bone metastases from solid tumors, including breast cancer.

A recent review of 34 trials performed in this patient population provided further confirmation that the use of bisphosphonates or denosumab (in addition to their other cancer treatments) reduces the risk of developing SRE and delay the time to SREs. However, questions on the optimal timing and duration of treatment with these agents in patients with bone metastases from breast cancer remain unanswered.(35) Bone-targeted agent therapy (i.e., bisphosphonates and denosumab) is actually recommended for patients with breast cancer with evidence of bone metastases.(36)

Patients with multiple, mainly osteoblastic lesions and pain syndrome may also benefit from treatment with radionuclide therapy. Bone-seeking radionuclides have been developed for palliation of bone pain from metastases.(37)

Metastron (strontium-89) and Quadramet (samarium-153 ethylene diamine tetramethylene phosphonate) have been approved in several countries for symptom palliation in patients with bone metastases.(38) The bone-seeking nature of these agents results in direct delivery of beta radiation to the sites of disease. Due to the long range of the beta particles from these radioisotopes, the major dose-limiting factor with this treatment modality is toxicity to the bone marrow cells, limiting the use of these agents to pain palliation only as they have not demonstrated an OS benefit. This toxicity has seriously limited their clinical use.

The limited hematological toxicity resulting from the short particle range of new alpha emitter radiopharmaceutical radium-223 dichloride may allow an easier integration with other anti-cancer therapies. Beside pain palliation effect, the high absorbed dose delivered by alpha-emitting radionuclides might have a direct antitumor effect in bone.

Multimodality therapy such as bisphosphonate/denosumab and radiopharmaceutical agents in addition to the anti-cancer treatment might offer superior symptom control and even prolonged progression-free and OS.

3.3 Study medications

3.3.1 Radium-223 dichloride

3.3.1.1 Drug development

Radium-223 dichloride solution for injection is a novel alpha particle emitting radiopharmaceutical. The bone targeting property of radium-223 is similar to that of other earth alkaline elements, like calcium or strontium-89. However, the radiation characteristics of an alpha particle emitting radionuclide appear to be more advantageous than of a beta-emitting radionuclide. Radium-223, with a physical half-life of 11.4 days, emits high linear energy transfer alpha radiation, with a range limited to less than 100 micrometers. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand deoxyribonucleic acid breaks in adjacent cells, resulting in an antitumor effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

Biodistribution studies have shown that radium-223 is selectively concentrated in bone compared to soft tissues, and that radium-223 is retained in the bone matrix.(39,40) Due to increased bone metabolism in skeletal metastases, preferential uptake in these lesions compared to normal bone is observed. A significant radium-223 antitumor effect has been demonstrated in an experimental skeletal metastases model in nude rats.(40)

The clinical development of radium-223 dichloride was initiated in August 2001. A phase I clinical study in subjects with skeletal metastases from breast and prostate cancer was performed to evaluate whether the product could be administered safely at therapeutically relevant doses. A total of 31 subjects were enrolled. Twenty-five subjects received a single intravenous (IV) injection in the dose escalating part of the study, with 5 subjects at each dose level of 46, 93, 163, 213 and 250 KiloBecquerel (kBq)/kg body weight radium-223 dichloride. The results of this phase I study were encouraging (low toxicity, significant pain relief, and decreased serum alkaline phosphatase [ALP]); thus, a phase II trial (BC1-02 study) for castration-resistant prostate cancer (CRPC) was conducted,(39) where subjects received multiple doses of either 50 kBq/kg body weight radium-223 dichloride or saline 4 times at 4-week intervals. In both studies, the results showed modest dose-dependent reversible hematological toxicity. No significant deleterious changes in chemistry parameters were seen, and the most frequent adverse event (AE) was transient diarrhea, which responded well to medication. In terms of efficacy, the BC1-02 phase II results showed a significant improvement in serum bone markers, i.e., bone ALP (a primary efficacy endpoint), and perhaps more importantly, a delayed time to prostate specific antigen (PSA) progression. Median OS at 2 years was 65.3 weeks for radium-223 dichloride and 46.3 weeks for placebo (HR = 2.1; p value=0.017 based on an intent-to-treat [ITT] population and adjusting for baseline covariates).

Following the positive results of the phase II trial, the phase III, double-blind, randomized, BC1-06, ALSYMPCA (**Al**pharadin in **Sym**ptomatic **P**rostate **Ca**ncer) trial was started in 2008. A total of 922 subjects with CRPC and symptomatic bone metastases were randomized to receive 6 injections of radium-223 dichloride (50 kBq/kg IV) or matching placebo every 4 weeks. Based on data of an interim analysis (n=809), the study was unblinded in June 2011, since radium-223 dichloride significantly improved OS compared to placebo (the median OS was 14.0 versus 11.2 months, respectively; HR=0.695; p=0.00185). Symptomatic skeletal events (SSEs) were lower in the radium-223 dichloride arm, and time to first SSE was significantly delayed (the median time to SSE was 13.6 months, versus 8.4 months, respectively; HR= 0.610; p=0.00046). A low incidence of myelosuppression was observed, with Grade 3/4 events of neutropenia (1.8%) and thrombocytopenia (6.2%). Adverse events of any grade were described in 88% of the subjects who received radium-223 dichloride, versus 94% in the placebo arm (Grade 3/4 AEs were described for 51% and 59%, respectively). The updated analysis (performed in June 2012) also showed that radium-223 dichloride significantly improved OS compared to placebo (median OS 14.9 versus 11.3 months, respectively; p=0.00007; HR=0.695).(41)

In an open-label, multicenter, single-arm, phase IIa study (BC1-09), 23 subjects with metastatic breast cancer with bone-dominant disease were administered 4 injections of radium-223 dichloride (50 kBq/kg IV) every 4 weeks. Bone markers were assessed at baseline, prior to every treatment, and thereafter at each follow-up visit. The primary efficacy endpoints were changed in urine levels of N-terminal telopeptide (NTX) and bone ALP from baseline at Week 16. Median urine NTX levels were reduced by 20% (from 36 to 29 nmo1 bone collagen equivalents (BCE)/mmo1 creatinine; p=0.03) and 33%(from 36 to 23 nmo1 BCE/mmo1 creatinine; p=0.0124) at Week 8 and Week 16, respectively; 17/23 and 9/13 subjects (for whom data were available) had a decrease in urine NTX at Week 8 and Week 16, respectively. Median bone ALP levels were reduced by 33% (from 22.1 to 12.1 ng/mL; p=0.0001) at Week 8 and 42% (from 22.1 to 10.94 ng/mL; p=0.04) at Week 16. Bone ALP levels were reduced in 20/22 subjects at Week 8 and in 10/12 subjects (for whom data were available) at Week 16. Radium-223 dichloride was found to be safe and well-tolerated. Three subjects had serious AEs (SAEs), none related to study drug; 1 of them died due to disease progression.(42)

Further details can be found in the Investigator's Brochure, which contains comprehensive information on the study drug.

3.3.1.2 Benefits 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 assess this potential.

3.3.1.3 Dosing rationale

The proposed dosing regimen in this phase II trial is 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) every 4 weeks for a 6-month treatment period (6 injections). In the completed phase I safety, tolerability, and pharmacokinetic (PK) clinical study (ATI-BC-1), subjects diagnosed with prostate or breast carcinoma and skeletal metastases were administered radium-223 dichloride in single doses of 46, 93, 163, 213, or 250 kBq/kg body weight (25 subjects) or multiple doses of 5 administrations of 50 kBq/kg body weight at 3-week intervals (3 subjects) or 2 administrations of 125 kBq/kg body weight at 6-week intervals (3 subjects). In the completed phase II study, 64 subjects with CRPC and painful skeletal metastases, received 4 injections of 50 kBq/kg body weight radium-223 dichloride (33 subjects) or placebo (31 subjects) at 4-week intervals, to examine the effects of radium-223 dichloride on biomarkers of disease progression, SSEs, pain palliation, survival, and safety parameters. The completed phase III trial, ALSYMPCA, enrolled 922 subjects diagnosed with CRPC and symptomatic bone metastases who received 6 injections of radium-223 dichloride (50 kBq/kg IV) in 4-week intervals. Endpoints included OS, time to disease-related events, TTP as measured by serum PSA and total ALP concentrations, pain palliation, acute and long-term safety profile, and health-related quality of life (HRQoL). The efficacy and safety data from the ALSYMPCA trial support the selection of a dosing regimen of 6 doses of 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) of radium-223 dichloride at 4-week intervals. This dose and schedule was determined to be efficacious, with only minor side effects and no indication of cumulative effect on bone marrow suppression following multiple administrations of radium-223 dichloride.

Currently, no data are available to assess if similar effects could be achieved with a dose lower than 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update).

The same dose was used in a phase II breast cancer study BC-109 which provided preliminary evidence of the effects of radium-223 on bone markers, Brief Pain Index – Short Form (BPI-SF) score, and tumor metabolism assessed by serial F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging and supports further investigations to confirm effectiveness of radium-223 in treating bone metastases in patients with breast cancer and bone-dominant disease. Data were communicated at the San Antonio Breast Cancer Symposium 2011 and published in 2014.(42) The study results are presented in detail in Section 3.3.1.1.

3.3.2 Study treatments exemestane and everolimus

Exemestane is an irreversible steroidal AI that has demonstrated efficacy in the treatment of postmenopausal patients with breast cancer. Beside its use in the adjuvant setting, exemestane is also indicated in the metastatic setting for postmenopausal patients with hormone receptor positive disease that has progressed following tamoxifen therapy (in the US) or following anti-estrogen therapy (in Europe). In a study of exemestane versus megestrol acetate in postmenopausal women who experienced failure of tamoxifen, exemestane demonstrated improvement in median OS (74.6 weeks for exemestane versus 55.0 weeks for megestrol acetate).(43)

In the first-line setting, a phase III study comparing exemestane versus tamoxifen showed that exemestane is an effective and well-tolerated first-line hormonal treatment for postmenopausal women with metastatic disease and resulted in a significant early improvement in time to tumor progression (9.9 months [95% confidence interval or CI: 8.7 to

11.8 months] for exemestane versus 5.8 months [95% CI: 5.3 to 8.1 months] for tamoxifen).(44) The major limitation of endocrine therapy remains however the development of therapeutic resistance, which will ultimately result in disease progression and eventual death in the majority of patients.

The activation of the mTOR pathway is thought to be a driving factor for endocrine resistance in breast cancer. The evidence of this proposed mechanism of resistance is based on the finding that the PI3K/Akt/mTOR pathway is constitutively activated in AI-resistant and long-term estrogen deprived breast cancer cells.

Everolimus, a rapamycin derivative, is an mTOR inhibitor. The strategy of dual inhibition by combining an endocrine agent (exemestane) with an mTOR inhibitor (everolimus) has been proven to be efficacious. Data from the phase III BOLERO-2 study showed that the addition of everolimus to exemestane significantly improved PFS compared with single-agent exemestane in ER+, HER2-negative patients whose metastatic disease was refractory to prior treatment with letrozole or anastrozole. (See Section 3.2 for a more detailed summary of the efficacy results).

The most common Grade 3 or 4 AEs in the everolimus + exemestane group versus placebo plus exemestane group were as follows: stomatitis (8% versus 1%), anemia (6% versus <1%), dyspnea (4% versus 1%), hyperglycemia (4% versus <1%), fatigue (4% versus 1%), and pneumonitis (3% versus 0%).The efficacy and safety results led to the recent marketing approval of everolimus by the FDA and EMA for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following an NSAI.

3.4 Study rationale

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 postmenopausal 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.

Primary efficacy endpoints

Symptomatic skeletal event-free survival is defined as the time from randomization to the occurrence of one of the following:

(1) An on-study SSE, which is defined as:

a. the use of EBRT to relieve skeletal symptoms
b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
c. the occurrence of spinal cord compression
d. a tumor related orthopedic surgical intervention.

(2) Death from any cause

Since the definition for measuring skeletal events will not use pre-specified imaging assessments, the use of imaging to identify a fracture or spinal cord compression will be triggered by symptoms. As such, only symptomatic events will be captured; asymptomatic radiographic events are not included in this composite endpoint. A delay or a reduction of SSEs represents an immediate clinical benefit, as it will delay or reduce bone pain, functional impairment, and the need for surgical intervention.

In ALSYMPCA, treatment with radium-223 dichloride increased the time to first SSE from 9.8 months to 15.6 months (HR 0.658, p=0.00037, data on file).

The median SSE-FS in ALSYMPCA was 9.0 and 6.4 months with and without radium-223 dichloride, respectively (HR = 0.685, p=0.00004). An ad hoc analysis (data on file) in subjects who did not receive docetaxel prior to radium-223 dichloride indicated that the median duration of SSE-FS is preserved in this subgroup of 395 subjects (SSE-FS was 9.5 months with and 6.7 months without radium-223 dichloride).

The occurrence of SREs in breast cancer patients with bone metastases is associated with worse functional, physical and emotional status and a decreased overall quality of life.(45,46) Prevention of SREs is, therefore, an important aim in the therapeutic management of these patients. Bone-targeted agents such as bisphosphonates and denosumab have been reported to delay the time to SRE and reduce the risk of developing SREs. In addition, they also reduced bone pain and showed an improvement in quality of life.(34,35,46,47,48,49) As per the American Society of Clinical Oncology treatment guidelines, they are both recommended in patients with breast cancer with evidence of bone metastases.(36)

A recent study in patients with bone metastases also reported that patients rated chronic pain as their main symptom and the most relevant HRQoL issue related to their disease. This was followed by difficulty in carrying out their usual tasks and worries about loss of independence and mobility.(50)

The high incidence of bone metastases as well as the prognostic relevance of bone involvement, definitely suggest that improvements in a bone-targeted therapeutic approach could provide further patient benefit.

In conclusion, SSE-FS is an objective variable that is likely to predict clinical benefit in the proposed study populations.

4. Study objectives

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.

The **primary endpoint** is:

- SSE-FS

The **secondary endpoints** are:

- OS
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline worst pain score (WPS) ≤8)
- Time to cytotoxic chemotherapy
- rPFS
- Pain improvement rate
- 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 SSE
- Time to bone ALP progression
- Bone ALP response at Week 12 and 4 weeks (± 7 days) after last radium-223 dichloride/placebo dose
- Bone-specific rPFS
- Resource utilization
- Biomarker assessments
- Time to visceral metastases onset (in subjects with no visceral disease at baseline).

*Safety endpoints were reported/measured as AEs. Acute safety was documented as the incidence of TEAEs. Long-term safety was documented as the incidence of post-treatment AEs. Hematopoietic reserve for tolerability of subsequent chemotherapy was assessed via the incidence of treatment emergent hematological toxicity and the incidence of post-treatment chemotherapy-related AEs.

Note: After implementation of **CSP Amendment 9**, subjects who completed the EOT visit could be transferred to a separate extended safety follow-up study for their remaining follow-up. After implementation of **CSP Amendment 10**, all such subjects will be transferred; only subjects on oral treatment will remain on study, and no post-treatment data will be collected beyond the 30-day safety follow-up (EOT visit).

As the key efficacy objectives will have been accomplished, long-term safety transferred, and only a limited number of subjects will remain in this study, in order to reduce the burden to study subjects, collection of data will be reduced and will focus mainly on **acute safety, SSE,**

and OS. Once subjects are rolled over, the long-term safety will be collected and assessed entirely in the separate extended safety follow-up study.

5. Study design

5.1 Design overview

This study is a phase II, randomized, double-blind, placebo-controlled, parallel group trial of radium-223 dichloride versus placebo administered with exemestane and everolimus and supportive care in subjects with HER2 negative hormone receptor positive breast cancer with bone metastases. 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.
- Visceral disease: Yes versus No

This study will be conducted at approximately 160 investigative study sites and approximately 311 subjects will be enrolled.

5.1.1 Study periods and duration

Prior to the primary analysis, the study period comprised of 4 periods: screening, randomization, treatment, and the follow-up period (active follow-up with clinic visits and active follow-up without clinic visits). After the primary analysis (after implementation of Amendment 10), the follow-up will be conducted in the separate extended safety follow-up study, therefore, upon discontinuation of oral treatment, subjects will be directly transitioned to the aforementioned study. For additional details, please refer to Section 15.6.

After Primary Analysis (after implementation of Amendment 10)

Following the administrative data review (per Amendment 8, see Section 10.5), conducted on DEC 2017 by a small group of unblinded Sponsor employees, independent of the study team, subject enrollment in this trial was discontinued on APR 2018.

Screening period:

All trial related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form (ICF). The screening period will consist of multiple evaluations that will take place within 3 weeks prior to randomization to ensure that all eligibility criteria are met (Section 6).

Randomization:

After all screening assessments have been completed and the subject's eligibility has been confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with radium-223 dichloride (Arm A - investigational arm) or placebo (Arm B - control arm). All subjects will receive open-label study treatment with exemestane and everolimus and supportive care as per the local/institutional standard of practice.

Treatment period:

The total treatment period is defined from the day of randomization until 4 weeks after the last administration of study treatment (radium-223 dichloride/placebo and exemestane and everolimus, whichever occurs last).

The study treatment consists of up to 6 cycles of radium-223 dichloride 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) (Arm A) or placebo (Arm B) each separated by an interval of 4 weeks ±7 days, in combination with exemestane and everolimus followed by ongoing treatment for all subjects with exemestane and everolimus, as applicable.

Subjects enrolled in the current study, will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving exemestane and everolimus prior to study entry are not eligible.

Treatment with exemestane and everolimus will continue after completion of radium-223 dichloride until disease progression, initiation of new anti-cancer therapy, unacceptable toxicity occurs, discontinuation of study treatment for other reasons, or study is terminated, whichever occurs first. All subjects receive supportive care, as per local standard of practice.

All ongoing subjects at the time of study termination will finish all study treatments as part of the study.

At the time of implementation of protocol Amendment 10, all subjects have already completed the radium-223 dichloride/placebo treatment.

During the treatment period, subjects will be assessed for safety at each treatment visit, every 8 weeks, and will be evaluated for radiologic progression according to local standard practice.

All SSEs should be recorded until end of treatment visit, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).

Subjects who can no longer travel to the clinical site and subjects who miss 2 consecutive treatment visits, will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study.

Subject management, unless otherwise defined by this protocol, will be in accordance with the local standard of practice.

Study treatments (radium-223 dichloride/placebo administration and exemestane and everolimus in all subjects) will continue until one of the study treatment withdrawal criteria (see Section 6.3.1) is met.

Follow-up period:

Note: Following primary analysis, the follow-up will be conducted in the separate extended safety follow-up study (please refer to the section below); therefore, upon discontinuation of oral treatment, subjects will be directly transitioned to the aforementioned study. For additional details, please refer to Section 15.6.

Long-term follow-up – Extended safety follow-up study

All study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, will be transitioned into a separate extended safety follow-up study (BAY 88-8223 study 16996 / NCT02312960). The separate extended safety follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in

the course of Bayer-sponsored clinical trials. The primary objective of this study is to define the long-term safety profile of radium-223 dichloride. All subjects who transition into this separate extended safety follow-up study will require a separate signed informed consent. All efforts will be made to transition all subjects to the extended safety follow-up study.

After primary analysis, sites/subjects not transitioning to extended safety follow-up protocol will be encouraged to report all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, new primary malignancies, bone fractures, and bone associated events via Bayer Pharmacovigilance as individual case safety report (ICSR), including the corresponding study number and subject ID.

This study will end by the time last subject on treatment discontinues oral exemestane and/ or everolimus treatment and completes end of treatment visit or discontinues from this study for another reason (e.g., death, consent withdrawn and active objection for further data collection, lost to follow-up). Until the transition to the extended safety follow-up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

5.1.2 Study endpoints

Primary Endpoint: The primary endpoint is SSE-FS.

Symptomatic skeletal event-free survival is defined as the time from randomization to the occurrence of one of the following:

(1) An on-study SSE, which is defined as:

a. the use of EBRT to relieve skeletal symptoms

b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)

c. the occurrence of spinal cord compression

d. a tumor related orthopedic surgical intervention.

(2) Death from any cause

Note: Any EBRT or orthopedic surgery related to a previous SSE but administered after signature of the ICF will not be counted as an on-study SSE.

Secondary Endpoints:

- OS
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline WPS ≤8)
- Time to cytotoxic chemotherapy
- rPFS
- Pain improvement rate
- Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy*

Exploratory Endpoints:

- Time to first on-study SSE

- Time to bone ALP progression
- Bone ALP response at Week 12 and 4 weeks (± 7 days) after last radium-223 dichloride/placebo dose
- Bone-specific rPFS
- Resource utilization
- Biomarker assessments
- Time to visceral metastases onset (in subjects with no visceral disease at baseline)

*Safety endpoints were reported/measured as AEs. Acute safety was documented as the incidence of TEAEs. Long-term safety was documented as the incidence of post-treatment AEs. Hematopoietic reserve for tolerability of subsequent chemotherapy was assessed via the incidence of treatment emergent hematological toxicity and the incidence of post-treatment chemotherapy-related AEs.

Note: After implementation of **CSP Amendment 9**, subjects who completed the EOT visit could be transferred to a separate extended safety follow-up study for their remaining follow-up. After implementation of **CSP Amendment 10**, all such subjects will be transferred; only subjects on oral treatment will remain on study, and no post-treatment data will be collected beyond the 30-day safety follow-up (EOT visit).

As the key efficacy objectives will have been accomplished, long-term safety transferred, and only a limited number of subjects will remain in this study, in order to reduce the burden to study subjects, collection of data will be reduced and will focus mainly on **acute safety, SSE, and OS.** Once subjects are rolled over, the long-term safety will be collected and assessed entirely in the separate extended safety follow-up study.

5.2 Primary variables

The primary variable is SSE-FS. The definition for this variable is provided in Section 5.1.2.

5.3 End of study

All study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, will be transitioned into a separate extended safety follow-up study (BAY 88-8223 study 16996 / NCT02312960). The separate extended safety follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The primary objective of this study is to define the long-term safety profile of radium-223 dichloride. All subjects who transition into this separate extended safety follow-up study will require a separate signed informed consent. All efforts will be made to transition all subjects to the extended safety follow-up study.

After primary analysis, sites/subjects not transitioning to extended safety follow-up study will be encouraged to report all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, new primary malignancies, bone fractures, and bone associated events via Bayer Pharmacovigilance as individual case safety report (ICSR), including the corresponding study number and subject ID.

This study will end by the time the last subject on treatment discontinues oral exemestane and /or everolimus treatment and completes end of treatment visit or discontinues from this study for another reason (e.g., death, consent withdrawn and active objection for further data

collection, lost to follow-up). Until the transition to the extended safety follow-up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

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 311 subjects with HER2 negative hormone receptor positive breast cancer with bone metastases will be randomized.

Eligibility

Eligibility is confirmed at the end of the screening period. At that time, the subject is randomized and enters the treatment period. 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 21-day window) may need the screening procedures to be repeated 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:

1. 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.
2. 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) or other validated in situ hybridization (ISH) assay for detection of HER2 gene expression.

3. 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.
4. 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.
5. Documentation of menopausal status: postmenopausal subjects or premenopausal subjects with ovarian radiation or concomitant therapy with a luteinizing hormone-releasing hormone (LH-RH) agonist/antagonist are eligible.
   - **Premenopausal** subjects with ovarian radiation or concomitant treatment with an LH-RH agonist/antagonist must have a plasma/serum estradiol assay within local laboratory postmenopausal range at screening, performed 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 physicians (please refer to Section 8.1.2).
   - **Postmenopausal** 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 a plasma/serum estradiol assay within local laboratory postmenopausal range, performed within 7 days of randomization,
     - bilateral ovariectomy.
6. Subjects with bone-dominant disease with at least 2 skeletal metastases identified at baseline by technetium-99m 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.
7. Measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. All disease burdens 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 technetium-99m 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 technetium-99m bone scans done within 3 weeks prior to randomization are acceptable.

   The FDG 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 ^{18}F-sodium fluoride 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.

8. Subjects must have experienced recurrent/progressive disease following treatment with a non-steroidal aromatase inhibitor (letrozole or anastrozole) in an adjuvant or metastatic setting.
9. 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 progressive disease at time of switch, will be counted as one line although 2 different agents have been administered.
10. 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 will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo.
11. Subjects must have experienced no more than 2 SREs prior to study entry defined as: Need for EBRT to bone, pathological bone fracture (excluding major trauma), spinal cord compression, and/or orthopedic surgical procedure. Subjects with no prior SREs are not permitted.

    Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization. Separate SRE events are the ones that occur at least 21 days apart from each other to ensure that linked events (eg, surgery to repair a fracture or multiple doses of radiation during a course of treatment) are not counted as separate events. In case of bone pain that occurs in several anatomical locations and requires separate EBRT sessions for the different anatomical locations, it should be counted as one event if the EBRT sessions are administered within a period of 21 days.
12. Subjects must be on therapy with bisphosphonates or denosumab for at least 1 month before start of study treatment.
13. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1
14. Life expectancy ≥6 months
15. Laboratory requirements:
    - Absolute neutrophil count ≥1.5 x 10^9/L
    - Platelet count ≥100 x10^9/L without platelet transfusion within 4 weeks prior to randomization
    - Hemoglobin (Hb) ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin within 4 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

- Pulse oximetry O_2 saturation >92% if lung metastases are present
- Creatinine ≤1.5 x ULN
- Estimated glomerular filtration rate ≥30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula (Note: please refer to local labeling for administration of full dose of bisphosphonates)
- International normalized ratio of prothrombin time (INR) and partial thromboplastin time (PTT) or activated PTT ≤1.5 x ULN at study entry. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) 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 for anticoagulants that require their monitoring as per local label.
- Serum albumin >30 g/L

16. Able to swallow oral medication

6.2 Exclusion criteria

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

1. 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/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.
2. Patients with immediately life-threatening visceral disease, for whom chemotherapy is the preferred treatment option.
3. Lymphangitic carcinomatosis
4. Patients with ascites requiring paracentesis within 2 weeks prior to study entry (signature of informed consent) and during the screening period
5. Subjects with inflammatory breast cancer
6. 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.
7. 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).
8. 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.

9. 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.
10. Prior treatment with radium-223 dichloride
11. 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.
12. Prior systemic radiotherapy with strontium-89, samarium-153, rhenium-186, or rhenium-188
13. ECOG PS ≥2
14. Blood transfusions, platelet transfusions or use of erythropoietin within 4 weeks prior randomization.
15. Use of biologic response modifiers, such as granulocyte macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF), within 4 weeks prior to randomization
16. Treatment with an investigational drug or with any anti-cancer treatments not permitted by the protocol, within the 4 weeks prior to randomization
17. Chronic conditions associated with non-malignant abnormal bone growth (e.g., confirmed Paget's disease of bone)
18. 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
19. Previous assignment to treatment in this study
20. Breast-feeding women
21. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride, exemestane, and everolimus or to other rapamycin derivatives
22. Subjects who received prior treatment or are already receiving everolimus treatment prior to study entry are not eligible
23. Known presence of osteonecrosis of the jaw

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.

6.3 Withdrawal of subjects from study

6.3.1 Withdrawal

Until the primary analysis, the study comprised the following 4 periods:

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

Note: *Study drug 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.*

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 subjects do not wish to be followed up further, they should sign the "*Declaration of Objection to 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.

6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

The total treatment period is defined from the day of randomization until 4 weeks after the last administration of study treatment (radium-223 dichloride/placebo and exemestane and everolimus, whichever occurs last).

Subjects *must* be withdrawn from the radium-223 dichloride/placebo treatment for the following reasons:

- If, in the Investigator's opinion, continuation of the radium-223 dichloride/placebo treatment would be harmful to the subject's well-being.
- If the subject experiences unacceptable toxicities to radium-223 dichloride/placebo.
- If a subject experiences National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 4 anemia, neutropenia, or thrombocytopenia lasting >2 weeks despite adequate supportive care treatment.
- If a subject experiences any non-hematological Grade CTCAE Grade 4 toxicity lasting >1 week despite adequate treatment.

- Delay in radium-223 dichloride/placebo administration of >4 weeks (maximum of 8 weeks between 2 injections of radium-223 dichloride/placebo).
- If the subject starts treatment with a prohibited metastatic breast cancer therapy (Section 8.1).
- If exemestane and everolimus or further standard of care hormonal anti-cancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued.
- After primary analysis, if the subject can no longer travel to the clinical site, she will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study (16996). Subjects who miss 2 consecutive treatment visits will be considered unable to travel to the site, will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study (16996).
- At her own request or at the request of her legally acceptable representative.
- At the specific request of the sponsor and in liaison with the Investigator (e.g., obvious non-compliance, safety concerns).

Subjects *must* be withdrawn from the exemestane and everolimus treatment for the following reasons:

- If, in the Investigator's opinion, continuation of exemestane and/or everolimus treatment would be harmful to the subject's well-being.
- If the subject experiences disease progression or initiates a new anti-cancer therapy. Disease progression being defined as radiological progression (either by RECIST or bone progression), or clinical progression.
- If the subject experiences unacceptable toxicities to exemestane and/or everolimus (as per Section 7.4.6 Dose adjustments, delays, and treatment discontinuations).
- Delay in exemestane and everolimus administration of >4 weeks.
- If the subject starts treatment with a prohibited metastatic breast cancer therapy (Section 8.1).
- If the subject can no longer travel to the clinical site. After primary analysis, she will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study (16996). Subjects who missed 2 consecutive treatment visits will be considered unable to travel to the site, will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study (16996)
- At her own request or at the request of her legally acceptable representative.
- At the specific request of the sponsor and in liaison with the Investigator (e.g., obvious non-compliance, safety concerns).

Subjects who experience disease progression (bone or non-bone) will discontinue exemestane and everolimus.

Note: *Study treatment discontinuation (i.e., withdrawal from treatment period) does not constitute withdrawal from the study.* Following primary analysis, the follow-up will be conducted in the separate extended safety follow-up study; therefore, upon discontinuation of

oral treatment, subjects will be directly transitioned to the aforementioned study. For additional details, please refer to Section 15.6.

6.3.1.2 Withdrawal from treatment period and/or all follow-up (no further data collection)

Subjects *must* be withdrawn from the study treatment and/or procedures and no further data will be collected for the following reasons:

- Subject withdraws consent from study treatment and/or study procedures. A subject must be removed from the study at her own request or at the request of her legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further the subject's rights will be protected.
- Subject is lost to follow-up
- Death

Note: *Withdrawal of consent should be documented in the subject's medical file. If the subject does not wish to be followed up further, they should sign the "Declaration of Objection to Collection of Study Data after Withdrawal of Consent" form.*

6.3.2 Replacement

Withdrawn subjects will not be replaced.

6.4 Subject identification

A subject number (a unique identification number) will be assigned via an Interactive Voice/Web Response System (IXRS) when a subject signs the ICF and is evaluated for inclusion into the study. When the subject is eligible for the trial, the study site will send an order (using the IXRS) to the manufacturer for drug shipment based on the planned visit date of the subject. See Section 7.2.

7. Treatments

7.1 Treatments to be administered

Investigational medicinal product (IMP): Radium-223 dichloride, 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) will be administered IV as a slow bolus injection for a maximum of 6 cycles at intervals of 4 weeks.

Reference therapy: A solution of isotonic saline (0.9% sodium chloride solution for injection) will be administered IV as a slow bolus injection 6 times, at intervals of 4 weeks.

Treatment with exemestane and everolimus: All subjects will receive exemestane and everolimus. Subjects enrolled in the current study, will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving exemestane and everolimus prior to study entry are not eligible. The dose of exemestane administered in the study is one 25-mg tablet once daily after a meal, which is the dose approved in US and Europe in advanced breast cancer. The recommended dose of everolimus administered in the study is 10 mg once daily with or without food, which is the dose approved in US and Europe in advanced breast cancer, in combination with exemestane. Starting dose, dose modifications,

and administration of exemestane and everolimus must be in compliance with the local labels in each of the participating countries and/or in line with local standard of practice.

Study treatment with exemestane and everolimus will continue after completion of radium-223 dichloride/placebo or until disease progression, initiation of new anti-cancer therapy, unacceptable toxicity occurs, discontinuation of study treatment for other reasons, or study is terminated, whichever occurs first.

Non-investigational medicinal products:

- ***Bone-targeted agents, Bisphosphonates or Denosumab:*** All subjects will receive therapy with bisphosphonates or denosumab at the time of study entry (for at least 1 month prior to start of radium-223 dichloride/placebo start). Subjects should be maintained on bisphosphonate or denosumab therapy throughout the study, unless, in the Investigator's opinion, these treatments will need to be discontinued. Bisphosphonates or denosumab should be administered as per the local label instructions and according to local standard of care. Changes in therapy should be done as per the Investigator decision.
- ***Other therapies:*** Supportive care therapies should be administered in line with local standard of care.

Please refer to Section 8.1 on prior and concomitant therapy concerning prohibited and allowed concomitant treatments during the radium-223 dichloride/placebo administration.

7.2 Identity of study treatment

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs provided by the sponsor, a system of numbering in accordance with all requirements of Good Manufacturing Practices (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance group. For all sponsor-supplied study drugs, lists linking all numbering levels will be maintained by the sponsor.

A complete record of batch numbers and expiry dates of all sponsor-supplied study treatment as well as the labels will be maintained in the sponsor study file.

7.2.1 Investigational medicinal product

7.2.1.1 Radium-223 dichloride

The alpha particle emitting radiopharmaceutical radium-223 dichloride is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride for IV administration. Radium-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 to 8.0. The radioactive concentration at the reference date is 1000 kBq/mL (1100 kBq/ mL after implementation of NIST update). 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 supplied with each shipment.

The sponsor will provide radium-223 dichloride which is manufactured by Bayer HealthCare. Radium-223 dichloride/placebo will be labeled according to the requirements of local law and legislation. Label text for all sponsor-supplied study drugs will be approved according to the sponsor's agreed procedures.

The product is produced according to GMP. The product will be delivered in a glass vial, ready-to-use with a certified activity. Radium-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-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°C to 8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

For study sites in the US, it is possible to have patient ready dose (PRD) prepared by a radiopharmacy. Dose will be delivered to the sites in pre-filled syringes. Cardinal Health is the radio pharmacy that will dispense the PRD in the US.

It is important to note that, in general (unless otherwise agreed), in cases where study drug has been ordered, the time window for administration should be within 3 days of the planned treatment day. If administration must be postponed more than 3 days, replacement of the drug order is required.

7.2.1.2 Saline

Isotonic saline (0.9% sodium chloride solution for injection) will be provided by the study site. Traceability of the respective manufacturers and batches will be maintained in the respective preparation documentation and drug accountability logs.

For saline solution and supportive care treatment which will be provided to the subjects from the study site's commercial supply it is required at minimum that the assignment, batch numbers, and expiry dates are recorded. The use of saline is to be recorded and documentation retained at the study site with a copy provided for the sponsor study file.

7.2.1.3 Study treatment with exemestane and everolimus

Exemestane and everolimus will be provided with appropriate labeling to each study center by the sponsor. Subjects enrolled in the current study, will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects already receiving exemestane and everolimus prior to study entry are not eligible. Administration of exemestane and everolimus will be in accordance to the local label and/or in line with local standard of practice.

Everolimus, a rapamycin derivative, is an mTOR inhibitor, indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-breast cancer in combination with exemestane. It is supplied as tablets (2.5 mg, 5 mg, 7.5 mg, and 10 mg) and as tablets for oral suspension (2 mg, 3 mg, and 5 mg). The recommended dose of everolimus administered in the study is 10 mg once daily with or without food, which is the dose approved in US and Europe in advanced breast cancer, in combination with exemestane. Follow special handling and disposal procedures for anti-cancer pharmaceuticals as directed in the local label.

Exemestane is an irreversible steroidal AI that is indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. It is supplied as tablets 25-mg tablets. The dose of exemestane administered in the study is one 25-mg tablet once daily after a meal, which is the dose approved in US and Europe in advanced breast cancer. Follow special handling and disposal procedures for anti-cancer pharmaceuticals as directed in the local label.

Exemestane and everolimus should be stored according to the label text on medication shipped to your site. Storage requirements may vary by country.

Starting dose, dose modifications, and administration of exemestane and everolimus must be in compliance with the local labels in each of the participating countries and/or in line with local standard of practice.

These treatments will be captured in the eCRFs.

7.2.2 Non-investigational medicinal products

7.2.2.1 Bone-targeted agents, bisphosphonates and denosumab

Bisphosphonates (diphosphonates) are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases including bone metastases. Whichever bisphosphonate is selected for use as therapy should be stored and administered according to the local label.

Denosumab (Xgeva®), a RANKL inhibitor, is indicated for the prevention of SREs in subjects with bone metastases from solid tumors. It is supplied as a single-use vial as a suspension of 120 mg/1.7 mL and should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days, as directed in the label.

Bisphosphonates or denosumab will be supplied by the study site and administered as part of the standard of care for the subject according to the local label.

7.3 Treatment assignment

To accomplish random assignment of radium-223 dichloride/placebo treatment, a computer-generated randomization list will be prepared by the sponsor and provided to the IXRS. The IXRS will assign each eligible subject a randomization number and the respective treatment in a ratio of 1:1 to radium-223 dichloride/placebo. In addition, 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), and visceral disease yes versus no.

The IXRS will provide only the randomization number to the caller, i.e., blinded personnel, but not the assigned treatment. A confirmation e-mail containing the randomization number will be sent to the unblinded personnel who will have to log into IXRS in order to know the treatment arm assigned to the patient. The unblinded personnel will be responsible for preparing the study drug for the subject for the first administration. For US only, if a subject is allocated to radium-223 dichloride, the unblinded person will fax the shipment request to Cardinal Health for pre-filled syringe. The timing for the drug order should be based on the planned subject visit date. If the subject is allocated to placebo, the unblinded person at the study site will be responsible for providing saline corresponding to the IXRS treatment day.

This should not be made available before to avoid unblinding the subject and blinded study personnel.

Subsequent orders for each study drug administration will be made by calling the IXRS from the study site on the date of the previous injection. If, after ordering, the order needs to be cancelled or amended, the Investigator should contact their monitor immediately.

7.4 Dosage and administration

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

In general, the administration of radioactive drugs involves a potential risk for third parties, due to radiation from the subject and due to possible contamination by spilling urine or feces. When radium-223 dichloride has been injected intravenously into a subject, the risk for external radiation exposure to third parties is extremely low, due to the short range of the alpha particles (<100 µm) and the low portion of beta and gamma radiation. For these reasons the product can be administered on an out-patient basis. To minimize the risk of contamination, the subject and her caregivers will receive oral and written instructions regarding hygiene precautions to abide by after receiving the radioactive drug according to the investigational study site radiation protection guidelines. These instructions will be given to all subjects, as neither the Principal Investigator nor subject will know the assignment to radium-223 dichloride/placebo injections.

7.4.1 Dose calibration

Radium-223 dichloride can be measured in a normal dose calibrator instrument. When all the required written approvals for the use and handling of radium-223 dichloride from the Radiation Protection Agency/Agencies for the specific site have been received by the sponsor, a vial of radium-223 dichloride for technical use will be sent to the study site.

Different clinical study sites possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from site to site. Consequently, each site must perform the radium-223 dial setting on their relevant dose calibrator(s) if no isotope calibration factor for radium-223 is being provided by the vendor of the dose calibrator. For dial setting, the clinical study site will receive a sealed vial or a pre-filled syringe containing a radium-223 solution for calibration only. The vial or syringe is identical to the vials/syringes used for study treatment. The amount of radium-223 in the vial/syringe 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.

As of Amendment 3, NIST has established an updated standardization for radium-223 dichloride, which indicates that an approximately 10% difference existed between activity values obtained using the current standard and the updated standardization. The current NIST standard for radium-223 dichloride (NIST 2010 [52]) will remain in effect for this protocol until all Health Authorities for which Bayer holds a marketing application for radium-223 dichloride have approved the regulatory variations for Xofigo®, anticipated Q 2 2016. All sites will be notified by Bayer when regulatory approvals are in place and the updated NIST standardization is to be implemented. Upon notification, and prior to the implementation, all sites will need to add a new dial-setting to their dose calibrators for the new NIST standardization for radium-223 dichloride (NIST update [53]), which should be documented on the appropriate study forms. This step will be performed so that all sites will have the new dial setting (NIST update [53]) in place at the time of implementation. The current dial

setting (NIST 2010 [52]) will be used until the worldwide global implementation date anticipated for Q 2 2016.

The change in the NIST radium-223 standard has no impact on subjects; subjects are receiving, and will continue to receive, the same actual dose and volume that was studied in ALSYMPCA 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. Subjects who are on-treatment at the time the new NIST reference standard goes into effect will be notified of this change and will be required to sign a Patient Information Sheet to acknowledge that they have received information on the updated NIST standard calibration. All patients randomized after the new reference standard is in effect will sign a revised ICF that contains the updated NIST standardization. The formula for the calculation of the volume to be administered has to be changed respectively.

7.4.2 Radium-223 dichloride dose handling

At least 2 unblinded personnel should be nominated at each study site (Section 7.5). The primary dedicated unblinded person ("the unblinded person"), who has the responsibility delegated from the Principal Investigator, will be responsible for the safe handling and storage of radium-223 dichloride and placebo control. The unblinded person also has the responsibility of correctly receiving and recording the delivery of radium-223 dichloride in accordance with this protocol. At least one deputy unblinded person should also be nominated. Radium-223 dichloride should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides.

The radium-223 dichloride vials or PRDs must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production or prior to the expiry date specified for PRDs.

Control measurements of both the radium-223 dichloride vial (before and after dispensing) and syringes (before and after administration) are performed as part of the clinical trial documentation. Since PRDs will be prepared at the country depot, relevant procedures are recorded by the country depot staff. All administrations of radium-223 dichloride will be based on the certified activity of radium-223 at the reference date. Please note that all documentation that contains unblinded information should be kept by the unblinded person(s) and not shared with the other study site personnel during the conduct of the study.

7.4.3 Radium-223 dose calculation

The dosage of radium-223 dichloride is 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update). The total activity to be injected will be calculated volumetrically using the subject's body weight within 5 days of injection (kg), the 50 kBq/kg (55 kBq/kg after implementation of NIST update) dosage level, and the decay correction factor (DK) to correct for physical decay of radium-223. A table with DKs according to physical decay of the study medication will be provided with each vial of radium-223 dichloride. The total amount (volume to be drawn into the syringe) to be administered to a subject should be calculated according to the recommended formula below:

$$\frac{\text{Body weight (kg)} \times 50\ \text{kBq/kg}^{a}}{\text{DK} \times 1000\ \text{kBq/mL}^{b}} = \text{volume to be injected (mL)}$$

[a] 55 kBq/kg after implementation of NIST update
[b] 1100 kBq/mL after implementation of NIST update

Site specific volume calculation methods are acceptable as well, provided that the subject dose is 50kBq/kg (55 kBq/kg after implementation of NIST update).

Data regarding activity, calculations, and volume to be injected must be recorded in the IMP preparation log and in the study electronic data capture tool (Medidata Rave; [RAVE]) by the unblinded person. This applies to both doses that are prepared at the study site and doses that are prepared by an off-site vendor.

For subjects in Arm B (placebo injection), the volume of saline to be injected will be provided by the IXRS based on the subject's weight. Data regarding the saline batch number and the volume to be injected should be recorded in RAVE.

7.4.4 Study drug dose preparation

To keep the treating physician blinded to the assignment of study medication, the unblinded person (e.g., from the hospital pharmacy or nuclear medicine department) will be responsible for blinding the syringe, and responsible for calculating the required dosage. Data regarding activity and volume to be injected should be recorded in the IMP preparation log and in the appropriate eCRF, both of which will not be available to the treating physician. Copies of the vial label and the syringe serial number are to be attached with each entry in the IMP preparation log. Additional written instructions for study drug administration, for blinded and unblinded personnel, will be provided.

Personnel should use appropriate protective clothing and equipment during syringe filling and application to prevent contamination with the radioactive solution (lab coats, medical gloves / protective glasses) and to reduce radiation exposure. Sites should adhere to all relevant radiation safety regulations as prescribed by local authorities administering their site radiation license, including as low as reasonably achievable principles.

Filling of the syringe should take place in a safety bench or similar cabinet in the Radiopharmacy/Nuclear Medicine department. The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe. The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy. In some countries/study sites a 3rd party vendor will be used to prepare the injections to be used by the study site.

Radium-223 dichloride should not be diluted or mixed with any solutions. If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a subject.

To maintain traceability, each subject will be assigned 1 syringe label set, with a unique serial number. The serial number will link the vial/batch received with the preparation and blinded administration of the syringe.

For subjects in the placebo arm, a syringe with isotonic saline will be prepared in the same way as for the active treatment, including the use of unique serial numbers on the syringe.

The study medication will be administered as a slow bolus IV injection. The actual radioactivity administered must be within the tolerance limits of ± 10% of the calculated radioactivity. After administration, the equipment used in connection with the preparation

and administration of drug, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for the handling of radioactive material and according to local laws. Written information about radium-223 dichloride and instructions for the handling and injection of radioactive material will be provided to study personnel.

7.4.5 Dose administration

In this subject population, disease progression is expected. Expected symptoms in this population are: bone pain, fatigue, nausea, anorexia, depression, constipation (also secondary to opioids, hematological complication as well as additional visceral metastases.

Chemotherapy is not permitted during treatment with radium-223 dichloride/placebo. If such treatment is necessary, then radium-223 dichloride/placebo treatment must be stopped. If possible cytotoxic chemotherapy should not be given before a 4 week washout period after last administration of radium-223 dichloride/placebo, provided the subject's bone marrow is not compromised.

Every effort will be made to administer the full dosing regimen. Single dose level adjustment of radium-223 dichloride/placebo is not permitted. Treatment delays or discontinuations of radium-223 dichloride/placebo may be instituted for the AEs described in Section 7.4.6 and dose adjustments, treatment delays, or discontinuations of treatment with exemestane and everolimus may be instituted according to the local label and/or local standard of practice.

7.4.6 Dose adjustments, delays, and treatment discontinuations

Radium-223 dichloride/placebo administration may be delayed by no more than 4 weeks (maximum 8 weeks between 2 injections) for recovery of AEs. If administration is delayed for >4 weeks (maximum 8 weeks between 2 injections), radium-223 dichloride/placebo administration should be discontinued.

Adverse events will be reported and graded according to NCI-CTCAE version 4.03.

7.4.6.1 Radium-223 dichloride dose delays and treatment discontinuations guidance

Myelosuppression

Changes in hematology parameters may occur after injection of study drug.

Neutropenia: In case of NCI-CTCAE Grade 3 to 4 neutropenia, the study drug administration should be delayed until recovery to Grade 2 (minimum absolute neutrophil count [ANC] 1.0 x 10^9/L) or better before next study drug administration.

Thrombocytopenia: In case of thrombocytopenia NCI-CTCAE Grade 2 to 4, the study drug administration should be delayed until recovery to CTCAE Grade 1 (minimum subjects with a platelet count 75 x 10^9/L) or better before next study drug administration.

Anemia: In case of anemia NCI-CTCAE Grade 3 to 4, the study drug administration should be delayed until recovery to CTCAE Grade 2 (minimum Hb 8.0 g/dL) or better before next study drug administration.

If a subject experiences CTCAE Grade 3 to 4 anemia, neutropenia or thrombocytopenia lasting >2 weeks in spite of adequate treatment, the subject must be discontinued from treatment with radium-223 dichloride/placebo.

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

Gastrointestinal events

Diarrhea: No prophylactic treatment for diarrhea is recommended. Anti-diarrheals can be used when needed. A further dose of study medication should not be given before diarrhea has recovered to CTCAE Grade ≤1.

Nausea/Vomiting: No prophylactic treatments for nausea or vomiting are recommended, but anti-emetic drugs can be used when needed. A further dose of study medication should not be given before nausea/vomiting has recovered to CTCAE Grade ≤1.

Constipation: Subjects can continue laxative as concomitant medication, but start of prophylactic treatments before study drug injection is not recommended. Laxative can be used when needed. A further dose of study medication should not be given before constipation has recovered to CTCAE Grade ≤1.

Fatigue

In cases of NCI-CTCAE Grade 3 to 4 fatigue, study drug administration should be delayed until recovery to Grade ≤1 before the next study drug administration.

Osteonecrosis of jaw

There is no specific radium-223 dose modification guidance for patients who develop osteonecrosis of jaw during radium-223 treatment. The management plan of individual patients who develop osteonecrosis of jaw in the course of the study should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in osteonecrosis of jaw, and in accordance with the local labeling of denosumab and bisphosphonates.

Non-pathological fractures

For traumatic fracture in weight bearing bones during treatment phase, the study drug administration should be delayed 2 to 4 weeks from the time of fracture.

Other toxicities

If a subject experiences any non-hematological NCI-CTCAE Grade 4 toxicity lasting >1 week despite adequate treatment subject will have to discontinue radium-223 dichloride/placebo treatment.

Exemestane

The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Other reported effects include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia, and peripheral and leg edema. Thrombocytopenia and leucopenia have been reported occasionally. Reductions in bone mineral density can occur with long-term use of exemestane.

Based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non-life-threatening AEs, dosage adjustment does not appear to be necessary. All local label directions must be followed.

Dose adjustment for everolimus due to adverse reactions

In the clinical experience in advanced breast cancer, the most common adverse drug reactions, with an incidence ≥10%, reported in association with everolimus plus exemestane therapy were: stomatitis, rash, fatigue, decreased appetite, diarrhea, dysgeusia, nausea, pneumonitis, weight decreased, epistaxis, and thrombocytopenia. Stomatitis was reported more than 5-fold compared to the placebo arm (64.5% vs. 10.9%). Hemorrhages were seen twice as often as in the placebo group (19.5% vs. 8.9%). The most common Grade 3 to 4 adverse drug reactions, with an incidence ≥2% were: stomatitis, hyperglycemia, pneumonitis, anemia, fatigue, elevated ALT, thrombocytopenia, elevated AST, dyspnea, and neutropenia.

Sites must follow all the local label recommendations in each participating country.

The following dose modifications for everolimus, based on the US and EU label guidance, are provided below as a general recommendation.

All label specific instructions for treatment with exemestane and everolimus will apply. Please refer to the local full prescribing information for further guidance.

Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of everolimus therapy. For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily.

Table 7–1 summarizes dose adjustment recommendations for specific adverse reactions.

Table 7–1: Everolimus dose adjustment recommendations

Adverse reaction	Severity[a]	Everolimus dose adjustment
Non-infectious pneumonitis	Grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1. Re-initiate everolimus at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt everolimus until symptoms resolve to Grade ≤1. Consider re-initiating everolimus at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue everolimus.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate everolimus at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at 5 mg daily.
	Grade 4	Discontinue everolimus.

Table 7–1: Everolimus dose adjustment recommendations

Adverse reaction	Severity[a]	Everolimus dose adjustment
Other non-hematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at same dose. If toxicity recurs at Grade 2, interrupt everolimus until recovery to Grade ≤1. Re-initiate everolimus at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating everolimus at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue everolimus.
Metabolic events (e.g., hyperglycemia, dyslipidemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate everolimus at 5 mg daily.
	Grade 4	Discontinue everolimus.
Thrombocytopenia	Grade 2 (<75, ≥50 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1 (≥75 x 10^9/L). Re-initiate everolimus at same dose.
	Grade 3 and 4 (<50 x10^9/L)	Temporary dose interruption until recovery to Grade ≤1 (≥75 x 10^9/L). Re-initiate everolimus at 5 mg daily. For sites based in Europe the additional dose modifications per local label are required.
Neutropenia	Grade 2 (≥1 x 10^9/L)	No dose adjustment required.
	Grade 3 (<1, ≥0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2 (≥1 x10^9/L). Re-initiate everolimus at same dose.
	Grade 4 (<0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2 (≥1 x10^9/L). Re-initiate everolimus at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25 x10^9/L) and no fever. Re-initiate everolimus at 5 mg daily.
	Grade 4	Discontinue everolimus.

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03

7.4.7 Supportive care guidelines

Ancillary Treatment (guidelines)

- Persistent neutropenia (Neutrophils/Granulocytes CTCAE Grade 4 [<0.5x10^9/L]) without fever: These subjects may be started on G-CSF 5 µg/kg/d subcutaneously (SC) until the neutrophil count has reached the local hospital's reference range.
- Neutropenia with fever (Neutrophils/Granulocytes CTCAE Grade 3 to 4 [<1x10^9/L]; fever >38.5°C): Blood cultures will be obtained and the subject started on empiric antibiotics for as long as clinically indicated. It is highly recommended that the

subject receive G-CSF 5 µg/kg/day subcutaneously until the neutrophil count has reached the local hospital's reference range with 2 separate measurements, at least 12 hours apart.

- Severe thrombocytopenia (CTCAE Grade 4 [<25.0x10^9/L]) or bleeding with CTCAE Grade 3 to 4 thrombocytopenia (<50.0x10^9/L): multiple platelet transfusions may be required to maintain platelet count ≥75 x 10^9/L if clinically indicated to control bleeding. Epsilon aminocaproic acid may be given to subjects with mucosal bleeding and platelet count CTCAE Grade 3 to 4.
- Severe anemia (Hemoglobin CTCAE Grade 3 [<80x10^9 g/L; 8.0 g/dL; 4.9 mmol/L]): Subjects will be transfused with packed red cells to maintain Hb value >80 g/L; 8.0 g/dL; 4.9 mmol/L if clinically indicated. Treatment with erythropoietin is allowed between study drug administrations for treatment of anemia.
- During treatment with denosumab or bisphosphonates, the subjects should be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

Subjects must be treated according to the local standard of practice and local label requirements for exemestane and everolimus. Known and theoretical interactions of everolimus with selected inhibitors and inducers of CYP3A4 and P-glycoprotein are listed in Appendix 16.6. Please refer to the local full prescribing information for further guidance.

7.5 Blinding

Every effort will be made to keep the study blinded. Subjects will be randomized to receive radium-223 dichloride/placebo in a double-blind fashion. All subjects will also receive exemestane and everolimus. This treatment will be provided by the sponsor and will be administered in an open-label format.

Due to the nature of radium-223 dichloride, there must be at least 2 persons in the study site's nuclear medicine department who are unblinded to the treatment arms assigned to subjects. One of these unblinded individuals will serve as back-up for the other. To maintain the study blind for the hospital personnel who provide treatment to the subject, the unblinded person at the study site will be responsible for filling the syringe with the correct amount of radium-223 dichloride/placebo (saline) and labeling it. Both radium-223 dichloride and placebo are clear solutions, thus syringes with radium-223 dichloride and placebo cannot be distinguished from each other visually. The person performing the administration of study drug must be blinded to the treatment arm. The subject will not be told whether they have received radium-223 dichloride/placebo. All treating physicians, clinical staff, subjects, and sponsor personnel will be blinded as to the treatment to which a subject is randomized, except for named representatives who will perform the verification of the drug accountability at the study sites and drug ordering.

Treatment with exemestane and everolimus is not blinded.

Unblinding:

In compliance with applicable regulations, in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see Section 9.6.1.4), the subject's treatment code will usually be unblinded before reporting to the Health Authorities, ethic committees if the SUSAR was related to the blinded treatment. Investigators may only unblind subjects under emergency unblinding rules. If a subject is unblinded by the Investigator, they must discontinue study drug(s).

Investigators should note that the occurrence of an SAE or PD should not routinely precipitate the immediate unblinding of the label.

If emergency unblinding is necessary for the treatment of a subject for an SAE, the study treatment can be unblinded via the IXRS system (refer to the IXRS manual for instructions). The participating site has unrestricted and immediate access to break the treatment code in IXRS. Should the blind code be broken for a subject, the medical monitor or designee should be contacted by the Principal Investigator within one working day of unblinding to discuss the rationale for the premature unblinding.

Following the primary analysis, the study will be fully unblinded.

7.6 Drug logistics and accountability

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

In some countries/study sites, it will be required to use a 3rd party vendor to prepare the injections to be used by the study site. A log of study medication (received, administered to subjects, and destroyed) must be maintained and signed by the dedicated person responsible for drug handling at each site. Any labels or mandatory logs provided by the sponsor are to be utilized according to instructions. A copy of study drug documentation will be collected for the sponsor file.

The responsible study site personnel will use the study drug only within the framework of this clinical trial and in accordance with this protocol. Instructions for drug handling, logistics, and accountability will be reviewed with study staff prior to the initiation of the study. Summaries of these instructions are provided below.

For radium-223 dichloride:

Radium-223 dichloride will be shipped to study site upon IXRS shipment request. Lead times differ per country but the shipment will arrive at the study site one day before the planned treatment at the latest. The responsible unblinded study site personnel will confirm receipt of sponsor-supplied study drug via IXRS system.

The unblinded person at the study site is responsible for drug accountability. A dedicated unblinded person representing the sponsor will monitor the drug accountability logs. Receipt, distribution, and destruction of the study drug must be properly documented according to the sponsor's agreed and specified procedures. An unblinded monitor will review overall drug accountability and destruction per the study site documentation only. The remains of radioactivity and contaminated material (i.e., vials, syringes, containers) should be disposed of in accordance with the local regulations and the hospital procedure, respectively. A log of radium-223 dichloride (received, administered to subjects, and destroyed) must be maintained and signed and the appropriate eCRF pages completed by the unblinded person responsible for drug handling at each site.

For locally provided isotonic saline (placebo):

Isotonic saline (placebo) will be provided by the study site pharmacy. Drug accountability for saline will also be performed. At a minimum, storage conditions, dispensing, batch numbers, and expiry dates will be retained in the study site files. A log of isotonic saline (administered to subjects, and destroyed) must be maintained and signed and the appropriate eCRF pages

completed by the unblinded person responsible for drug handling at each site. The used vials must be stored until the drug accountability has been completed by the unblinded monitor.

For study treatment with exemestane and everolimus

Exemestane and everolimus will be shipped to the study center upon IXRS shipment request. The responsible site personnel will confirm receipt of sponsor-supplied study drug in writing and/or via IXRS. A log of this study medication (assigned, dispensed, administered to subjects, returned to site by subject, and destroyed) must be maintained and signed by the dedicated person responsible for drug handling at each center in addition to the completion of the appropriate pages of the eCRF. All study drug packages assigned (opened, unopened, or empty) must be stored until the drug accountability has been completed by the monitor.

7.7 Treatment compliance

Subjects will receive treatment with radium-223 dichloride under supervision of a physician licensed in the administration of radioisotopes. Unblinded study personnel will check the administration volume and total radioactivity injected. The dose activity and the volume injected will be recorded in a study drug log and the eCRF pages, neither of which will be available to the treating physician or site personnel. Only the unblinded monitor will review overall drug accountability and destruction per the site documentation.

8. Non-study therapy

8.1 Prior and concomitant therapy

At baseline screening, all prior cancer-related treatments are to be recorded.

All concomitant medications taken by the subject from signing of the ICF to 4 weeks after last study drug administration must be recorded in the eCRF. Thereafter, until the end of the active follow-up period, **only** medications given to treat **any grade AEs related to the study drug,** analgesic medication and any subsequent anti-cancer treatment medication need to be recorded in the eCRF.

The generic name and trade name of each prior or concomitant medication, its indication, dosage and, when applicable, the start and stop dates will be recorded.

The sponsor's representative will encode all therapy and medication according to well-recognized dictionaries of medical codes.

It is not required to report the administration of contrast media or radioactive tracer in conjunction with the protocol-specified radiological procedure (CT or bone scan) on the concomitant medications eCRF page unless there is an AE related to the administration of the contrast agent (e.g., an allergic reaction related to the administration of a contrast agent) or the tracer.

8.1.1 Prohibited concomitant therapy

Other cancer treatment with established efficacy in breast cancer except hormonal treatments should not be used during the treatment period. If such treatments are considered to be the best standard of care during the treatment period, further radium-223 dichloride/placebo administrations must be discontinued and the subject should enter the active follow-up period.

All supportive care for the subject may be provided at the discretion of the Investigator.

Note that all treatments for breast cancer, including other investigational drugs taken after withdrawal from treatment with radium-223 dichloride/placebo, will be recorded in the eCRFs until the end of the active follow-up period.

Concomitant therapy during the treatment phase of the study with any of the following listed is **prohibited**:

- Chemotherapy
- Radiopharmaceuticals such as strontium-89, samarium-153, rhenium-186, or rhenium-188
- Hemibody external radiotherapy
- Other investigational drugs
- All medications that are prohibited as per the local label instructions for exemestane and everolimus and the supportive treatment.
- It is the site responsibility to ensure that the study treatment with exemestane and everolimus is administered in line with standard practice and local label instructions. Same applies for bisphosphonates and denosumab.

8.1.2 Permitted concomitant therapy

The following therapies are considered **permissible** during the study treatment:

- Standard-of-care anti-cancer hormonal treatment: if exemestane and everolimus is no longer considered a treatment option and the subject must start another standard-of-care hormonal treatment, the subject can continue radium-223 dichloride/placebo until completion.
- Conventional multivitamins, selenium, and soy supplements
- All subjects are expected to have been on therapy with either denosumab or bisphosphonates for at least 1 month before the start of study treatment and to continue on this therapy during the course of the study, with no change to therapy expected during the study, except for toxicity reasons.
- During treatment with denosumab or bisphosphonates, the subjects should be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.
- In premenopausal women with ovarian suppression, treatment with LH-RH agonists or antagonists must start at least 4 weeks prior to enrollment (signature of informed consent) and continue during the treatment period. Non-hormonal methods of contraception should be employed during therapy until menses resume.
- Subjects of reproductive potential who are sexually active must agree to utilize, during the treatment period and for 6 months after last dose of radium-223 dichloride/placebo, 2 reliable and acceptable methods of contraception used simultaneously: a barrier method such as a) condoms (male or female) with spermicidal agent or b) diaphragm or cervical cap with spermicide, combined with a highly effective non-hormonal birth control method such as intra-uterine device (IUD).
- Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization (if required to ensure that the treatment range for Hb is met at

Day 1 of each cycle) but not within 4 weeks prior randomization. Platelet transfusions are allowed after randomization but not within 4 weeks of randomization.

- Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the Investigator. These drugs are not allowed within 4 weeks prior to randomization.
- Analgesic use will be captured via a subject diary and the eCRF (analgesic consumption diary and recorded analgesics, respectively, see schedule of assessments, Table 9–1). Subjects will be asked to track their analgesic use in an analgesic consumption diary for 24 hours prior to their clinic visit. Any medication taken for pain, whether for palliation of bone pain or relief of other type of pain, and any changes should be recorded in the eCRF at each visit. Note that EBRT treatment should be recorded in the eCRFs until end of the active follow-up period without clinic visits.
- Treatment with exemestane and everolimus: subjects enrolled in the current study, will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects who received prior treatment or are already receiving everolimus prior to study entry are not eligible. Administration of exemestane and everolimus will be in accordance to the local standard of practice and local label.

8.2 Post-study treatment therapy

Treatment with radium-223 dichloride/placebo will be halted following completion of the full assigned treatment or at early termination. Treatment with exemestane and everolimus will be terminated for disease progression or unacceptable toxicity or other reasons (Section 6.3.1.1).

Following discontinuation of all study treatments (radium-223 dichloride/placebo treatment, exemestane and everolimus), subjects will be treated and followed as per the institutional standard-of-care and/or according to the physician's clinical judgment.

If possible cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy or other investigational drug should not be given before a 4-week washout period after last administration of radium-223 dichloride/placebo, provided the subject's bone marrow is not compromised.

Details of post-study anti-cancer treatment will be recorded on the appropriate eCRF page.

9. Procedures and variables

9.1 Tabular schedule of evaluations

All laboratory analyses will be conducted by local laboratories.

Efficacy and safety measurements obtained during the course of the study are summarized in the schedule of assessments (Table 9–1).

Table 9–1: Schedule of assessments

Study Period	**Screening[a]**	**Randomization**	**Treatment[b,c]**											
			Radium-223 dichloride or Placebo + treatment of exemestane and everolimus									**Ongoing treatment of exemestane and everolimus**		**EOT visit**
Visit:	**0-1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 onwards (after primary analysis)**	
Cycle:	**-**	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**-**	**-**	**-**
Timing:	**3 wk pre-random.**		**C1, Day 1**	**C1, Day 15[d]**	**C2, Day 1**	**C2, Day 15**	**C3, Day 1**	**C3, Day 15**	**C4, Day 1**	**C5, Day 1**	**C6, Day 1**	**4 wk post-last Ra-223/ placebo dose**	**After primary analysis q8 wk, regardless of SSE status**	**4 wk post-last dose[e]**
Window (days):				**±3**	**± 7**	**±3**	**± 7**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**±7**	**± 7**
Informed consent[h]	X													
Subject ID assignment	X													
Review of eligibility	X													
Demographic data	X													
Medical history	X													
Disease history	X													
Prior SRE	X													
Randomization[a]		X												
BPI-SF[i]			X		X		X		X	X	X	X		
Resource utilization questionnaire			X		X		X		X	X	X	X		
AEs, SAEs, new 1° malignancies[j]	X		X	X	X	X	X	X	X	X	X	X	X	X
Prior and con meds[m]	X		X	X	X	X	X	X	X	X	X	X	X	X
Cancer-related tx[n]	X		X	X	X	X	X	X	X	X	X	X	X	X
Analgesic consumption diary[i, o]			X		X		X		X	X	X	X		
Record 24 h analgesic use[o]			X		X		X		X	X	X	X		
Record opiate use			X		X		X		X	X	X	X		
Vital signs[p]	X		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (according to local standard practice)	X						X			X		X		X
Weight (kg)	X		X[q]	X	X[q]	X	X[q]	X	X[q]	X[q]	X[q]	X[q]	X[q]	X
Height (cm)	X													

Table 9–1: Schedule of assessments

Study Period	Screening[a]	Randomization	Treatment[b,c]											
			Radium-223 dichloride or Placebo + treatment of exemestane and everolimus									Ongoing treatment of exemestane and everolimus		EOT visit
Visit:	**0-1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 onwards (after primary analysis)**	
Cycle:	**-**	**-**	**1**		**2**		**3**		**4**	**5**	**6**	**-**	**-**	**-**
Timing:	**3 wk pre-random.**		**C1, Day 1**	**C1, Day 15[d]**	**C2, Day 1**	**C2, Day 15**	**C3, Day 1**	**C3, Day 15**	**C4, Day 1**	**C5, Day 1**	**C6, Day 1**	**4 wk post-last Ra-223/ placebo dose**	**After primary analysis q8 wk, regardless of SSE status**	**4 wk post-last dose[e]**
Window (days):				**±3**	**± 7**	**±3**	**± 7**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**±7**	**± 7**
Physical examination[r]	X		X		X		X		X	X	X	X	X	X
ECOG PS	X		X		X		X		X	X	X	X	X	X
Hematology[s]	X[t]		X[u]	X	X[u]	X	X[u]		X[u]	X[u]	X[u]	X[u]	X[u]	X
Pregnancy test and estradiol assay[v]	X[t]		X		X		X		X	X	X	X	X	X
Clinical chemistry[w]	X[t]		X[x]	X	X[x]	X	X[x]		X[x]	X[x]	X[x]	X[x]	X[x]	X
Coagulation panel[y]	X		X		X		X		X	X	X	X		
Serum, plasma, and urine biomarkers[z]			X						X			X		
Whole Blood for CTCs[ii]			X		X		X		X	X	X			
Technetium-99m bone scan[aa,bb]	X	X												
Chest, abdominal and pelvic CT scan[aa,dd,ee]	X	X												
SSEs			X		X		X		X	X	X	X	X	X
Drug order[ff]		X	X		X		X		X	X	X	X	X	
Radium-223 Cl_2 or placebo injection[gg]			X		X		X		X	X	X			
Dispense exemestane + everolimus			X		X		X		X	X	X	X	X	
Drug accountability			X		X		X		X	X	X	X	X	

Abbreviations: AE = adverse event; BPI-SF = brief pain index-short form; Cl_2 = dichloride; CT = computed tomography; con med = concomitant medication; Cx, Dx = Cycle x, Day x; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; FDG = F-18 fluorodeoxyglucose; ID = identification number; IXRS = interactive voice/web response system; q = every; PET = positron emission tomography; SAE = serious adverse event; SSE = symptomatic skeletal event; tx = treatment; WBC = white blood cell.

a. All screening evaluations must be complete and reviewed prior to randomization. Screening evaluations must be complete within 3 weeks prior to randomization. If all screening data are available and the subject is eligible for the study, randomization may occur at the end of the screening visit.
b. All assessments at treatment visits should be performed before study drug administration.
c. Subjects will continue in the treatment period until disease progression or initiation of a new anti-cancer therapy, unacceptable toxicity occurs or subject discontinues study treatment for other reasons.
d. Any unscheduled visits are to be conducted in the same manner as visits described for Visit 12 onwards.
e. EOT follow-up visit will be conducted 4 weeks (±7 days) after last dose of study treatment (radium-223 dichloride/placebo and exemestane and everolimus) or after discontinuation from study treatment.
f. *Footnote deleted in Amendment 10.*
g. *Footnote deleted in Amendment 10*
h. Informed consent is to be collected before the initiation of any study related procedures.
i. Analgesic consumption diary and BPI-SF will be dispensed to the subject just the visit before Cycle 1, Day 1, Cycle 2, Day 1, Cycle 3, Day 1, Cycle 4, Day 1, Cycle 5, Day 1, Cycle 6, Day 1, Visit 11, and Visit 12. Additionally, PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire. After primary analysis, pain and QoL assessments will no longer be conducted.
j. Adverse events will be collected through 30 days post the last administration of study medications. Investigator should check for occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, any new malignancy.
k. *Footnote deleted in Amendment 10.*
l. *Footnote deleted in Amendment 10.*
m. At baseline screening, all prior concomitant medications, including analgesics, are to be recorded. Thereafter, collect all concomitant medications up to 4 weeks post-last study drug administration. Analgesic use has to be recorded via the analgesic concomitant medication case report form.
n. Record any cancer-related treatments.
o. At screening, an analgesic consumption diary will be dispensed to the subject. Subjects will be asked to record analgesic use 24 hours prior to their clinic visit. Pain medication will also be assessed at each visit by study site. Analgesic use will be recorded in the appropriate eCRF page.
p. The measurement of vital signs will include: blood pressure, heart rate, respiratory rate, and temperature.
q. Subject's weight should be re-checked prior to each injection to calculate appropriate drug dosing. At all sites, weight is to be taken only once for each dose and it should be measured within 5 days prior to dosing. For US sites using the central patient ready dose (PRD) depot only, the subject weight for the dose day must be reported in a timely manner to the country PRD depot to allow adequate time for the PRD preparation and delivery (approximately 2 days). All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments to avoid 2 pre-dose clinic visits.
r. A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.
s. Hematocrit, hemoglobin, platelet counts, red blood cells counts, white blood cell counts, white blood cell differential. Subjects with abnormal platelet count or WBC at EOT should be followed until resolution.
t. The screening clinical chemistry and hematology values are recommended to be measured within 1 week prior to randomization and the first injection should be done as soon as possible after randomization.
u. Blood sample for hematology must be taken, analyzed, and evaluated within the 5 days prior to each study drug administration.
v. Premenopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization, prior to each study drug administration (taken and evaluated within 5 days prior to administration) and EOT. Post-menopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test. A plasma/serum estradiol assay is required within 7 days prior to randomization in premenopausal women with radiotherapy ovarian ablation or medical ovarian suppression and postmenopausal women age <55 years and one year or more of amenorrhea and no ovarian suppression.
w. Sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, blood urea nitrogen (BUN) bilirubin (total), total cholesterol, triglycerides, and glucose.
x. Blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each study drug administration.

y. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) will be allowed to participate in the study if no underlying abnormality in coagulation parameters exists per prior history; weekly evaluation of PT-INR/PTT will be required until stability is achieved for anticoagulants that require their monitoring as per local label. Blood sample for coagulation tests must be taken and evaluated within 5 days prior to each study drug administration.
z. Blood and/or urine sample for exploratory evaluation of biomarkers, prior to radium-223 dichloride/placebo administration. Serum and plasma samples will be collected within 5 days of dosing at Cycle 1, Day 1, Cycle 4, Day 1, and Visit 11. Urine samples will be collected at Cycle 1, Day 1, Cycle 4, Day 1, and Visit 11. After primary analysis, biomarker samples will not be collected.
aa. After primary analysis, imaging scans will continue until until disease progression or treatment discontinuation according to local standard practice. Scans will be read locally. Please also refer to Section 9.2.6 and Appendix 16.2.
bb. 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.
cc. Footnote removed in Amendment 10.
dd. Chest/abdominal/pelvic magnetic resonance imaging will be accepted instead of chest/abdominal/pelvic computed tomography. FDG 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).
ee. To maintain a consistent evaluation of each subject, the same imaging technique and procedure must be used through the assessment periods. Any unexpected abnormality must be reported by the site personnel to the treating physician or the subject's general practitioner.
ff. IXRS drug (re-)supply order should be coordinated at each study visit to coincide with delivery prior to the subject's next scheduled study visit.
gg. The minimum time window between 2 injections of radium-223 dichloride/placebo must be 4 weeks.
hh. *Footnote removed in Amendment 10.*
ii. Details of sampling are described in the Laboratory Manual. Blood samples for analysis of circulating tumor cells will be collected within 5 days of Day 1 of Cycles 1 through 6 prior to study drug dosing. After primary analysis, the collection within 5 days of the EOT visit or disease progression will no longer be conducted.

9.2 Visit description

9.2.1 Screening period (Visit 0 to 1)

The screening period lasts from date of signature of informed consent until the date of subject randomization in IXRS. The screening period duration is 3 weeks.

Pre-treatment evaluations will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the signed consent has been obtained.

Standard-of-care imaging such as CT/MRI etc. performed within 3 weeks prior to randomization as well as routine bone scans performed within 3 weeks prior to planned dates of randomization will be accepted as baseline imaging if they meet protocol requirements (anatomic coverage, image acquisition as per RECIST 1.1 guidelines for CT/MRI scans). Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status including blood values will be recorded in the eCRF.

The following procedure and evaluations will be performed within 3 weeks prior to planned randomization unless otherwise specified:

- Sign informed consent
- Subject registration and subject number assignment via IXRS
- Review of inclusion and exclusion criteria and confirm eligibility
- Demographics
- Record medical history
- Record disease history: HER2 status can be determined by evaluating for HER2 over-expression using IHC and/or HER2 gene amplification using in situ hybridization, eg, FISH or CISH. For subjects with equivocal HER2 IHC (IHC 2+), it is recommended that HER2 status be confirmed using a validated assay for HER2 gene amplification.
- Record prior SRE
- Record AEs
- Record concomitant medications/therapy, including analgesics
- Record breast cancer-related treatment (prior and current)
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead electrocardiograms (ECG). Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection.
- Record height (cm) and weight (kg)
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems.
- ECOG PS

- Radiological tumor assessment:
  - A chest/abdominal/pelvic CT or MRI. This is not needed if standard-of-care chest/abdominal/pelvic CT or MRI images taken within 3 weeks prior to randomization are available.
  - A bone technetium-99m scan with careful identification of all disease-related hotspots. This is not needed if standard-of-care bone scan performed within 3 weeks prior to planned randomization date is available and in line with protocol requirements. Confirmatory scan using single photon emission tomography (SPECT)-CT/MRI or CT/MRI (with and without contrast media) should be obtained if not performed within 3 weeks prior to randomization. The field of acquisition should include all areas where bone lesions are present.
  - CT/MRI done as part of the standard of practice within 3 weeks of randomization and standard-of-care bone scans done within 3 weeks of randomization are acceptable.
  - FDG 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.

The following procedures and evaluations should be performed within 1 week prior to randomization. Results must be available, reviewed, and signed and dated by the Investigator prior to randomization.

- Blood draw for clinical chemistry: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), ALT, AST, lactate dehydrogenase (LDH), bone ALP (if testing is available and can be performed locally), serum creatinine, blood urea nitrogen (BUN), total bilirubin, total cholesterol, triglycerides, glucose, phosphate, and albumin.
- Blood draw for hematology: hematocrit, Hb, platelet counts, red blood cells (RBC) counts, white blood cell (WBC) counts, WBC differential.
- A coagulation panel: prothrombin time (PT), PTT, INR. Subjects treated with warfarin, heparin, enoxaparin, rivaroxaban, dabigatran, apixaban, or aspirin (e.g. ≤100 mg daily) 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 for anticoagulants that require their monitoring as per local label.
- Pregnancy test: premenopausal women must have a negative serum pregnancy test performed within 7 days prior to randomization. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Estradiol assay: a plasma/serum estradiol assay is required within 7 days prior to randomization in premenopausal women with radiotherapy ovarian ablation or medical ovarian suppression and postmenopausal women age <55 years and one year or more of amenorrhea and no ovarian suppression.

One week prior to randomization, the subject should be given a subject diary to be used for subject questionnaires and the analgesic consumption and should receive training in its use.

Important Note: If rescreening is indicated, it must be completed with approval from the medical monitor of the sponsor. No more than one rescreening attempt will be allowed for each subject. Please refer to Section 6.1 for further guidance on cases in which rescreening is allowed and the time window for rescreening.

9.2.2 Randomization

Randomization in the IXRS may occur only after the completion of the screening evaluations and confirmation of subject eligibility. Randomization may coincide with the end of a screening visit if all evaluations are complete; otherwise, randomization may be performed in a separate clinic visit.

- IXRS must be called for drug re-supply in preparation for the next study visit. This should be done on the day of randomization (where possible) to provide the maximum time in advance of the next scheduled subject visit date and in accordance with country-specific order lead-times.

9.2.3 Treatment period

The treatment period is defined from the day of randomization until 4 weeks (±7 days) after the last administration of study treatment (radium-223 dichloride/placebo and exemestane and everolimus whichever occurs last).

The time between randomization and first injection of radium-223 dichloride/placebo should be as brief as possible in accordance with the country-specific drug order lead time.

During the treatment period, the subject will visit the study site at regular intervals. Radium-223 dichloride/placebo will be injected at 4-week intervals for 6 cycles on an out-patient basis (Section 9.1). The minimum time window between 2 injections of radium-223 dichloride/placebo must be 4 weeks.

All subjects will receive treatment with exemestane and everolimus for breast cancer. Subjects enrolled in the current study, will start treatment with exemestane and everolimus, after randomization, either before or simultaneously to the first injection of radium-223 dichloride/placebo. Subjects who received prior treatment or are already receiving everolimus prior to study entry are not eligible. Administration of exemestane and everolimus will be in accordance to the local standard of practice and local label. Starting dose, dose modifications, and administration of exemestane and everolimus must be in compliance with the local labels in each of the participating countries and/or in line with local standard of practice.

Treatment with exemestane and everolimus will continue after completion of radium-223 dichloride/placebo until disease progression, initiation of new anti-cancer therapy, unacceptable toxicity occurs, discontinuation of study treatment for other reasons, or study is terminated, whichever occurs first.

All ongoing subjects at the time of study termination will finish all study treatments as part of the study.

It is the responsibility of the unblinded person to calculate the required volume of study drug (i.e., dose of radium-223 dichloride/placebo) for the subject based on the subject's body weight within 5 days of administration and the reference date of the received study medication (Section 7.4.3).

For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed 5 days prior to injection. All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments to avoid 2 pre-dose clinic visits.

Before administration of radium-223 dichloride/placebo, the subject must be well hydrated; thus, the subject should be instructed to drink *ad libitum*.

Hematology parameters requirements prior to study drug administration

The blood samples for clinical chemistry and hematology should be taken within 5 days before each study drug administration, and the hematology parameters must be evaluated before each study drug administration.

First radium-223 dichloride/placebo administration

Before the first administration of radium-223 dichloride/placebo (within 3 days), the ANC should be ≥1.5 x 10^9/L, the platelet count ≥100 x 10^9/L and Hb ≥ 8g/dL.

Blood transfusions and treatment with erythropoietin stimulating agents are allowed after randomization but not within 4weeks prior randomization. Platelet transfusions are allowed after randomization but not within 4 weeks prior to randomization.

Subsequent radium-223 dichloride/placebo between study drug administrations

The following hematological parameters value should be met prior to each subsequent radium-223 dichloride/placebo administration: Hb level ≥8.0 g/dL, ANC ≥1.0 x 10^9/L, and the platelet count ≥75 x 10^9/L.

If Hb levels are below 8 g/dL, the Hb needs to recover to 8.0 g/dL or higher before next study drug administration.

If ANC is lower than 1.0 x 10^9/L or platelet count is lower than 75 x 10^9/L, radium-223 dichloride/placebo injection should be delayed until recovery to ANC ≥1.0 x 10^9/L and platelet count ≥75 x 10^9/L.

If there is more than a 4-week delay in the next injection (i.e., more than 8 weeks between injections), the study drug should be permanently discontinued and the subject should enter the active follow-up period without clinic visits. Treatment of low Hb is acceptable between study drug administrations.

Treatment with exemestane and everolimus

Dose modifications for the treatment with exemestane and everolimus are summarized in Section 7.4.6. Please refer to the local full prescribing information for further guidance.

9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Assessments to be performed PRIOR to radium-223 dichloride/placebo ("study drug") administration:

- BPI-SF questionnaire will be completed the day of the visit, prior to any other study assessments/procedures and should be checked for completion at the visit. Additionally, PRO Questionnaire Information Sheet is to be completed by clinical staff based on discussion with patient, even if patient does not complete the BPI-SF questionnaire.

- Resource utilization questionnaire to be completed by site
- Record AEs, SAEs, and all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy.
  Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug
- Recording of analgesic use will be performed by:
  - Analgesic use recorded via the analgesic concomitant medication case report form
  - Analgesic consumption diary (completion to be checked by site) to be filled in by the subjects for 24 hours prior to the visit. The analgesic use for 24 hours prior to the visit will be recorded by the Investigator on the eCRF.
- Record opiate use
- Record concomitant medications/therapy
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- 12-lead ECG (Visit 6 [Cycle 3, Day 1] and Visit 9 [Cycle 5, Day 1]). Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection.
- Record weight (kg), within 5 days prior to dosing
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems (all abnormal findings must be reported in the AE eCRF pages).
- ECOG PS
- Blood draw for hematology evaluation (within 5 days before radium-223 dichloride/placebo administration): hematocrit, Hb, platelet counts, RBC, WBC, WBC differential. Results to be assessed and documented prior to study drug treatment. The Hb values need to be confirmed to be at least 8 g/dl prior to each dose. If blood is drawn the day of the administration of radium-223 dichloride/placebo, results must be available prior to study drug administration.
- Blood draw for clinical chemistry: Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), creatinine, BUN, bilirubin (total), total cholesterol, triglycerides, glucose, phosphate, and albumin (blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each study drug administration).
- A coagulation panel (blood sample to be taken and evaluated within 5 days prior to each study drug administration): PT, PTT, and INR.
- Pregnancy test: premenopausal women must have a negative serum pregnancy test performed and evaluated within 5 days before radium-223 dichloride/placebo administration. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.

- Blood draw and urine sample for exploratory biomarker analysis: Serum, plasma, and urine samples will be collected within 5 days of Visit 2 (Cycle 1, Day 1) and within 5 days of Visit 8 (Cycle 4, Day 1) prior to study drug dosing.
- Blood draw for analysis of circulating tumor cells (CTCs) collected within 5 days of Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6), prior to study drug dosing.
- Radiological tumor assessments: please refer to Section 9.2.6 and Appendix 16.2)
- Record SSEs. The Investigator will assess the subject for the following disease events:
  - Use of EBRT to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor related orthopedic surgical intervention
  - Spinal cord compression
    Note: Symptomatic skeletal events should be recorded until end of active follow-up, independent of whether the subject starts a new anti-cancer therapy (i.e., chemotherapy, other).
- Administer radium-223 dichloride/placebo.
- Dispense exemestane and everolimus
- Perform drug accountability

Assessments to be performed AFTER each injection of radium-223 dichloride/placebo:

- IXRS must be called for drug re-supply in preparation for the next study visit. This should be done on the day of the current treatment visit (where possible) to provide the maximum time in advance of the next scheduled subject visit date and in accordance with country-specific order lead-times.
- For US sites using the central PRD depot ONLY, the subject weight for the dose day must be reported to the country PRD depot in a timely manner to allow adequate time for the PRD preparation and delivery. The subject's weight measurement, order confirmation call to the IXRS, and prescription for the central PRD depot are to be performed 5 days prior to injection. All efforts should be made to measure weight at the same visit with the pre-dose laboratory assessments to avoid 2 pre-dose clinic visits.

9.2.3.2 Visits 3, 5 and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit)

Radium-223 dichloride/placebo will not be administered at these visits.

- Record AEs, SAEs, and all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy
  Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- Record concomitant medications/therapy, including analgesics
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature

- Record weight
- Blood draw for hematology evaluation: hematocrit, Hb, platelet counts, RBC, WBC, WBC differential. (Performed only at Visit 3 [Cycle 1, Day 15] and Visit 5 [Cycle 2, Day 15])
- Blood draw for clinical chemistry is only required at Visit 3 (Cycle 1, Day 15) and Visit 5 (Cycle 2, Day 15): Na, K, Cl, Ca, ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), creatinine, BUN, bilirubin (total), total cholesterol, triglycerides, glucose, phosphate, and albumin

9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards, and unscheduled visits)

Treatment with exemestane and everolimus will continue until disease progression, initiation of a new anti-cancer therapy, unacceptable toxicity occurs or subject discontinues study treatment for other reasons, or study is terminated, whichever occurs first. After the primary analysis, if the subject can no longer travel to the clinical site, she will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study (16996). Subjects who miss 2 consecutive treatment visits will be considered unable to travel to the site, will be discontinued from all study treatments and will be transitioned to the separate extended safety follow-up study (16996). All ongoing subjects at the time of study termination will finish all study treatments as part of the study.

During this period, clinic visits are to occur as follows:

- In all subjects Visit 11 will be performed after 4 weeks (±7 days) after last radium-223 dichloride/placebo dose
- After primary analysis, regardless of the occurrence of SSE, the visits from Visit 12 onwards will occur every 8 weeks ±7 days.

After primary analysis, the following procedures/evaluations should be performed at these visits (Visit 12 onwards and unscheduled visits):

- Record AEs, SAEs, and all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy.
  Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- Record concomitant medications/therapy
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature
- Record weight (kg), within 5 days prior to dosing
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems (all abnormal findings must be reported in the AE eCRF pages).
- ECOG PS

- Blood draw for hematology evaluation (within 5 days prior to each visit): hematocrit, Hb, platelet counts, RBC, WBC, WBC differential. Results to be assessed and documented prior to study drug treatment. The Hb values need to be confirmed to be at least 8 g/dL prior to each dose. If blood is drawn the day of the administration of study drug treatment, results must be available prior to study drug administration.
- Blood draw for clinical chemistry: Na, K, Ca, ALT, AST, creatinine, BUN, bilirubin (total), total cholesterol, triglycerides, and glucose (blood sample for clinical chemistry must be taken and evaluated within 5 days prior to each visit).
- Pregnancy test: premenopausal women must have a negative serum pregnancy test performed and evaluated within 5 days prior to each visit. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Record SSEs. The Investigator will assess the subject for the following disease events:
  - Use of EBRT to relieve skeletal symptoms
  - New symptomatic pathological bone fractures (vertebral and non-vertebral)
  - Tumor related orthopedic surgical intervention
  - Spinal cord compression
- Dispense exemestane and everolimus
- Perform drug accountability
- 12-lead ECG should be performed at Visit 11 and then every 8 weeks (±7 days), independently of the frequency of the visits. Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection. After primary analysis, ECGs should be done according to local standard practice.
- Radiological tumor assessment: please refer to Section 9.2.6 and Appendix 16.2.

9.2.3.4 End of treatment visit

An EOT visit will be performed within 4 weeks ±7 days post-discontinuation or completion of all study treatments. The following procedures/evaluations should be performed at this visit:

- Record AEs and SAEs for 30 days after the last treatment
  Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.
- All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs, if the criteria of SAE were met, regardless of the Investigator's causality assessment.
- Record all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy.
- Record concomitant medications/therapy
- Record breast cancer-related treatment
- Record vital signs: blood pressure, heart rate, respiratory rate, and temperature

- 12-lead ECG. Electrocardiograms should not be obtained when serum potassium is <3.5 mmol/L. Hypokalemia should be corrected prior to ECG collection. After primary analysis, ECGs should be done according to local standard practice.
- Record weight
- Perform full physical examination: A full physical examination must include the evaluation of head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal, and neurological systems (all abnormal findings must be reported in the AE eCRF pages).
- ECOG PS
- Blood draws for hematology (within 5 days of the visit): hematocrit, Hb, platelet counts, RBC counts, WBC counts, WBC differential
- Blood draws for clinical chemistry (within 5 days of the visit): Na, K, Ca, ALT, AST, creatinine, BUN, bilirubin (total), total cholesterol, triglycerides, glucose
- Pregnancy test (within 5 days of the visit): premenopausal women must have a negative serum pregnancy test. Postmenopausal women (as defined in Section 6.1) are not required to undergo a pregnancy test.
- Record SSEs
- Radiological tumor assessment: please refer to Section 9.2.6 and Appendix 16.2.

If subjects cannot travel to the clinical site due to deterioration of disease, the EOT visit will be replaced by a follow-up telephone call from the clinical site. Adverse events, information on all occurrences of leukemia, MDS, aplastic anemia, or any other new primary malignancy, as well as any anti-cancer therapies, will be discussed and captured in the eCRFs. Since this information will be collected over the telephone from the subject, it is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the subject and document it in the eCRF.

9.2.4 Active follow-up

Following primary analysis, the follow-up will be conducted in the separate extended safety follow-up study. Therefore, active follow-up is no longer applicable to this study (see Section 5.1.1 for further details).

9.2.5 End of study

All ongoing study subjects who have completed at a minimum the EOT visit or 30 days from last study treatment dose, whichever is latest, will be transitioned into an extended safety follow-up study (BAY 88-8223 study 16996 / NCT02312960). The separate extended safety follow-up study has been set up to follow subjects who received radium-223 dichloride or placebo in the course of Bayer-sponsored clinical trials. The primary objective of this study is to define the long-term safety profile of radium-223 dichloride. All subjects who transition into this separate long-term follow-up study will require a separate signed informed consent. All efforts will be made to transition all subjects to the extended safety follow-up study.

After primary analysis, sites/subjects not transitioning to extended safety follow-up study will be encouraged to report all occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, new primary malignancies, bone fractures, and bone associated events via Bayer

Pharmacovigilance as individual case safety report (ICSR), including the corresponding study number and subject ID.

This study will end at the time the last subject on treatment discontinues oral exemestane and /or everolimus treatment and completes end of treatment visit or discontinues from this study for another reason (e.g., death, consent withdrawn and active objection for further data collection, lost to follow-up). Until the transition to the extended safety follow-up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

9.2.6 Radiological assessment: tumor and response evaluation

Radiological scans for tumor evaluation must be performed at the following time points:

- Within 3 weeks prior to randomization: technetium-99m bone scan and CT or MRI (chest/abdomen/pelvis and any additional sites of disease, as applicable)

After primary analysis:

- CT or MRI (chest/abdomen/pelvis and any additional sites of disease, as applicable): according to local standard practice.
- Technetium-99m (bone scan): according to local standard practice.

Disease response assessment, using the modified RECIST 1.1 (mRECIST 1.1) guidelines (See also Appendix 16.2), is to be performed at each time point when CT/MRI scans are done.

This schedule is to be maintained and will not be shifted because of treatment interruptions/delays.

Standard-of-care CT/MRI done within 3 weeks of randomization and standard-of-care bone scans done within 3 weeks of randomization are acceptable provided they are in line with protocol requirements criteria (anatomic coverage chest/abdomen/pelvis and in line with RECIST 1.1/mRECIST 1.1 guidelines for image acquisition). All suspected sites of disease should be imaged.

After primary analysis, imaging scans will continue until disease progression or treatment discontinuation according to local standard practice.

Note: FDG 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).

A technetium-99m bone scan with careful identification of all disease-related hotspots should be performed for all patients at the above mentioned time points. All visible bone lesions must also be imaged with conventional anatomical imaging procedures such as CT or MRI scan (at time points when CT/MRI scans are done).

Note: 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.

The same lesions identified at baseline must be evaluated at follow-up assessments using the same technique and preferably by the same Investigator/radiologist.

For details on radiological tumor assessment please also refer to Appendix 16.2.

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

- Date of birth
- Age at randomization
- Race and ethnicity (where it is allowed by local regulation)

9.3.2 Medical history

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

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

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

The following other baseline characteristics will be collected:

- Date of breast cancer diagnosis
- Date of diagnosis of metastatic breast cancer
- Stage of breast cancer at diagnosis
- Treatment of breast cancer before enrollment (e.g., surgery, radiation, etc.)
- Weight (kg)
- Vital signs: blood pressure (mmHg), heart rate (beats per minute), respiratory rate (respirations per minute), and temperature (°C)
- ECOG PS
- Cancer pain assessment
- Laboratory assessments
    - Hematology: hematocrit, Hb, platelet counts, RBC, WBC, WBC differential
    - Clinical chemistry: Na, K, Cl, Ca, total cholesterol ALT, AST, LDH, bone ALP (if testing is available and can be performed locally), creatinine, BUN, total bilirubin, triglycerides, glucose, phosphate, and albumin

9.4 Efficacy

9.4.1 Efficacy variables

The primary efficacy variable is:

- SSE-FS

The secondary efficacy variables are:

- OS
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline WPS ≤8)
- Time to cytotoxic chemotherapy
- rPFS
- Pain improvement rate

The study will also include the following **exploratory efficacy endpoints**:

- Time to first on-study SSE
- Time to bone ALP progression
- Bone ALP response at Week 12 and 4 weeks (± 7 days) after last radium-223 dichloride/placebo dose
- Bone-specific rPFS
- Time to visceral metastases onset (in subjects with no visceral disease at baseline)

Note: After implementation of **CSP Amendment 9**, subjects who completed the EOT visit could be transferred to a separate extended safety follow-up study for their remaining follow-up. After implementation of **CSP Amendment 10**, all such subjects will be transferred; only subjects on oral treatment will remain on study, and no post-treatment data will be collected beyond the 30-day safety follow-up (EOT visit).

As the key efficacy objectives will have been accomplished, long-term safety transferred, and only a limited number of subjects will remain in this study, in order to reduce the burden to study subjects, collection of data will be reduced and will focus mainly on **acute safety, SSE, and OS**. Once subjects are rolled over, the long-term safety will be collected and assessed entirely in the separate extended safety follow-up study.

9.4.2 Definition of efficacy variables

9.4.2.1 Primary endpoint

Symptomatic skeletal event-free survival is defined as the time from randomization to the occurrence of one of the following:

(1) An on-study SSE, which is defined as:

a. the use of EBRT to relieve skeletal symptoms
b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
c. the occurrence of spinal cord compression
d. a tumor related orthopedic surgical intervention.

(2) Death from any cause

Note: All prior SRE-related procedures (i.e., orthopedic surgery, EBRT) must be administered prior to randomization.

9.4.2.2 Secondary efficacy endpoints

Overall survival is defined as the time (days) from the date of randomization to the date of death due to any cause. For subjects who are still alive, their OS will be censored at the last known alive date or the database cutoff date, whichever occurs first.

Time to opiate use for cancer pain is defined as the interval from the date of randomization to the date of opiate use. Subjects who have no opiate use at the time of analysis will be censored at the last assessment date of no opiate use. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Time to opiate use will be determined by analgesic use captured via subject diary and/or the eCRF (analgesic consumption diary and recorded analgesics, respectively, see schedule of assessments)**.**

Time to pain progression will be evaluated in subjects with baseline WPS ≤ 8.

Time to pain progression is defined as the interval from randomization to the first date a subject experiences pain progression based on WPS. Pain progression is defined as an increase of 2 or more points "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

OR

an increase in pain management (IPM) with respect to baseline, whichever occurs first.

Assessments will occur on the day of the visit. An evaluable pain assessment interval requires completion of a minimum of 4 out of 7 questions. Subjects who have not experienced pain progression at the time of analysis will be censored on the last post-baseline pain assessment date the subject was known to have not progressed. Subjects with no on-study assessment or no baseline assessment will be censored at the date of randomization.

Pain improvement is defined for subjects evaluable for pain improvement, i.e., subjects with baseline WPS≥2, as a 2-point decrease or more in WPS from baseline over 2 consecutive measurements conducted at least 4 weeks apart, without an IPM.

Pain improvement rate is defined as the number of subjects with pain improvement as defined above, divided by the total number of subjects evaluable for pain improvement (i.e., subjects with baseline WPS≥2). Pain improvement rate at week 12, EOT, and any visit will be considered.

The BPI-SF (Appendix 16.7 is a short, self-administered questionnaire with 11 items, which was designed to evaluate the intensity of, and the impairment caused by pain. All BPI-SF items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 ("no pain") to 10 ("pain as bad as you can imagine") numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) using 0 (does not interfere) to 10 (completely interferes) rating scales.

The items are aggregated into 2 dimensions, (1) Pain severity index, using the mean of the 4 items on the pain intensity, and (2) Function interference index, using the mean of the 7 pain interference items. All 4 severity items must be completed for aggregating the pain severity index. The function interference index is scored as the mean of the item scores multiplied by 7, given that more than 50% or 4 of 7, of the items have been completed.

Time to cytotoxic chemotherapy is defined as the time (days) from the date of randomization to the date of the first cytotoxic chemotherapy.

Radiological progression-free survival (rPFS) is defined as the time (days) from the date of randomization to the date of confirmed radiological progression in either soft tissue, viscera or bone, or death (if death occurs before progression). Subjects without confirmed radiological progression or death at the time of analysis will be censored at their last date of radiological tumor assessment (See Statistical Analysis Plan [SAP] for detailed censoring rules). Bone scans and CT/MRIs will be read locally. All bone lesions visible on a technetium-99m bone scan will need to also be imaged using conventional anatomical imaging techniques such as SPECT CT/MRI or CT/MRI (with or without contrast). Bone progression will be declared according to the modified RECIST 1.1 criteria (see Appendix 16.2). If a new bone lesion or unequivocal increase in size of bone lesions is identified on bone scan, the lesion must also be confirmed by CT/MRI. If a new bone lesion or unequivocal increase in size of bone lesions is only visible on a CT/MRI and not visible on a technetium-99m bone scan, progression will be declared without further confirmation.

9.4.2.3 Exploratory efficacy endpoints:

Time to first on-study SSE is defined as the time (days) from the date of randomization to the date of the first on-study SSE.

Time to bone ALP progression is defined as the time (days) from the date of randomization to the date of first bone ALP progression. Bone ALP progression is defined as ≥25% increase from the baseline value, at least 12 weeks from baseline in subjects with no bone ALP decline from baseline; or ≥25% increase above the nadir value, which is confirmed by a second value obtained 4 or more weeks later in subjects with an initial bone ALP decline from baseline.

Bone ALP response is defined as ≥30% reduction of the blood level at Week 12 and 4 weeks (± 7 days) after last radium-223 dichloride/placebo dose, compared to the baseline value. Confirmed bone ALP response is defined as a ≥30% reduction of the blood level, compared to the baseline value, confirmed by a second bone ALP value 4 or more weeks later.

Radiological progression-free survival based on bone imaging (bone-specific rPFS) is defined as the time (days) from the date of randomization to the date of confirmed radiological progression detected by bone imaging or death (if death occurs before progression). Subjects without confirmed radiological progression or death at the time of analysis will be censored at their last date of radiological tumor assessment. (See SAP for detailed censoring rules). Bone scans will be read locally. All bone lesions visible on a technetium-99m bone scan will need to also be imaged using conventional anatomical imaging techniques such as SPECT CT/MRI or CT/MRI (with or without contrast). Bone progression will be declared according to the modified RECIST 1.1 criteria (see Appendix 16.2). If a new bone lesion or unequivocal increase in size of bone lesions is identified on bone scan, the lesion must also be confirmed by CT/MRI. If a new bone lesion or unequivocal increase in size of bone lesions is only visible on a CT/MRI and not visible on a technetium-99m bone scan, progression will be declared without further confirmation.

Time to visceral metastases onset (in subjects with no visceral disease at baseline) is defined as the time (days) from the date of randomization to the date of the first scan showing visceral metastatic disease.

9.5 Pharmacokinetics

No PK measurements will be performed in this study. No PK interaction is expected between radium-223 dichloride and the co-administered exemestane and everolimus therapy. Radium-223 is an isotope and is therefore not metabolized. There are no hints that radium is involved in any transporter process. The main portion of radioactivity is excreted with the feces. The liver seems not to be involved in the excretion of radium-223 or its decay products. They are directly excreted into the small intestine. The co-administered products are typical small molecules that are metabolized in the liver. Thus, no direct impact of radium-223 on the PK of the co-administered products is expected.

9.6 Safety

The Investigator(s) and the sponsor's representative will review the safety data throughout the course of the study. The following safety variables will be evaluated:

- Adverse events: AEs will be collected and recorded on an ongoing basis throughout the study as described in Section 9.6.1.
- Safety variables: Safety variables will include the analysis of acute and long-term effects and the appearance of new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy. Please refer to Section 5.1.2 for further information. The complete list of variables to be analyzed for this study will be provided in the Statistical Analysis Plan (SAP).
- Laboratory assessments: The following laboratory assessments with reference ranges, including Investigator determinations, will be recorded in the source documentation and the eCRF:
  - Hematology: hematocrit, Hb, platelet counts, RBC, WBC, WBC differential.
  - Clinical chemistry: Na, K, Ca, total cholesterol, ALT, AST, serum creatinine, BUN, total bilirubin, total cholesterol, triglycerides, and glucose.
  - A coagulation panel: PT, PTT, and INR.

All subjects who receive at least one dose of study drug will be valid for safety analysis. All AEs will be reported and graded according to NCI-CTCAE v4.03. Laboratory evaluations, vital signs, changes in physical examination findings will also be assessed.

9.6.1 Adverse events

9.6.1.1 Definitions

Adverse event

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 subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

Adverse event versus medical history

In the following differentiation between medical history and AEs, the term "condition" may include abnormal physical examination findings, symptoms, diseases, laboratory findings, or scans.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are considered 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 considered as **medical history** (e.g., allergic pollinosis).
- Symptoms that were present prior to signing of informed consent but for which the diagnosis was confirmed after signing of informed consent should be documented as **medical history**.
- Conditions that started or deteriorated after signing of informed consent will be documented as **adverse events**.

Serious adverse event (SAE)

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

a. Results in death

b. Is life-threatening

   The term "life-threatening" in the definition refers to an event in which the subject 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 in-subject 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 functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the Investigator

g. Is an occurrence of any additional malignancies including AML or hematological conditions such as MDS, aplastic anemia, myelofibrosis (regardless of the Investigator's causality assessment). If disease progression leads to signs and symptoms that meet the criteria for seriousness (e.g., hospitalization), the associated signs and symptoms should be reported as SAEs, not the underlying cause (i.e., "progressive disease" should not be recorded as an SAE). In this case disease progression should be mentioned on the SAE form as an "alternative explanation."

An isolated laboratory abnormality that meets the criteria for CTCAE Grade 4 classification is not reportable as an SAE, unless the Investigator assesses that the event meets standard International Conference on Harmonisation criteria for an SAE. All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on the laboratory eCRF (including values reported from central laboratories).

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the Investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE should be documented using the NCI-CTCAE v4.03, JUN 2010; see Section 16.1.

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Causal relationship of the study treatment exemestane and everolimus and concomitant medication of interest, bisphosphonates or denosumab, will also be collected.

Possible answers are "yes" or "no"

An assessment of "no" would include:

- The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical study site,

  or

- 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.

Important 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 subject's 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 PK of the study treatment: The PK properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics (PD) 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".

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below:

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

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 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

9.6.1.3 Assessments and documentation of adverse events

All AEs occurring from the time the subject signs the ICF until 30 days after the last dose of study medications must be recorded on the eCRF. Treatment-emergent AEs and all SAEs that occur during the treatment period and up to 30 days after the last administration of study treatments must be reported on the appropriate eCRF.

All SAEs that occur during the treatment period and up to 30 days after the last administration of study treatments must immediately (within 24 hours of the Investigator's awareness) be reported in the appropriate eCRF. If more than one AE occurs, each event should be recorded separately. All AEs and SAEs are to be followed until resolved or as clinically required.

All AEs and SAEs occurring beyond 30 days after the end of study treatment must be documented and reported if considered to be related to study medications or to study related procedures.

Subjects who receive cytotoxic chemotherapy during the follow-up period will be followed up for the development of febrile neutropenia and hemorrhage during their chemotherapy treatment and for up to 6 months after chemotherapy. Occurrence of these AEs must be documented and reported if considered to be related to the chemotherapy treatment.

However, all occurrences of additional malignancies including AML, and hematological conditions such as MDS, aplastic anemia, myelofibrosis must be reported as SAEs, regardless of the Investigator's assessment.

Note: Specifically for this study, relevant symptoms related to SSEs should be reported as AEs independent of the timing of occurrence (prior to 30 days after last dose of study treatment or after this interval) or relationship with study drug.

All bone fractures and bone associated events (e.g., osteoporosis) should be collected as either AEs or SAEs if the criteria of SAE were met, regardless of the Investigator's causality assessment.

Adverse events may be reported spontaneously by the subject or elicited through open (non-leading) questioning during each visit to the clinic and at the end of the active follow-up period without clinic visits. As far as possible, all AEs must be described by their duration (start and stop date), severity (graded according to the CTCAE v4.03), relationship to treatment, and according to the need of other specific therapy. All information will be recorded in the source documentation and AE eCRF.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the trial), requiring treatment, causing apparent clinical manifestations, or judged as relevant by the Investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates (onset and resolution of event), intensity, temporal and causal relationship to investigational product and/or protocol related procedures, possibly alternative factors (comorbidities, co-medications), therapeutic action taken, result of

therapeutic action, and ultimate outcome of the AE. The Investigator's assessment of AEs and laboratory results with grades and causality assessments must be documented and retained in the source documentation. If more than one AE occurs, each event should be recorded separately. All AEs and SAEs are to be followed until resolved or as clinically required.

9.6.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (e.g., hospitalization), the associated signs and symptoms should be reported as an SAE, not the underlying cause (i.e., "progressive disease" should not be recorded as an SAE). **In this case, disease progression should be mentioned on the SAE form as "alternative explanation".**

Reporting of additional malignancies

All occurrences of any additional malignancies including AML, and hematological conditions such as MDS, aplastic anemia, myelofibrosis must be reported as SAEs, regardless of the Investigator's causality assessment

Investigator's notification of the sponsor

All Investigators will be thoroughly instructed and trained on all relevant aspects of the Investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the Investigator Site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 9.6.1.3 must immediately (within 24 hours of the Investigator's awareness [or the next working day for weekends and public holidays]) be reported to the contact at the contract research organization (CRO), as detailed in the study manual. An SAE form must also be completed within 24 hours of the Investigator awareness (or the next working day for weekends and public holidays) and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by the submission of updated reports to the designated recipient.

Additionally, all occurrences of MDS, aplastic anemia, or any other new primary malignancy such as acute myeloid leukemia must be reported as SAEs at any time, and regardless of the Investigator's causality assessment (Section 9.6.1.3). All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs, if the criteria of SAE were met, regardless of the Investigator's causality assessment. Grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as SAEs, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If Investigators are in doubt about the applicable reporting obligations, they should consult with the medical monitor.

For subjects who die >30 days after the administration of the last study treatment, submission of the AE page of the eCRF is not required. However, the SAE Complementary Form should be submitted to the applicable Bayer HealthCare Pharmacovigilance department if the death is considered related to study treatment. In addition, this death information will also be collected in the end of active follow-up page of the eCRF.

Serious AEs occurring after the protocol defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the independent ethics committees/institutional review boards

Notification of the independent ethics committees/institutional review boards (IECs/IRBs) about all relevant events (e.g., SAEs, SUSARs) will be performed by the sponsor and/or by the Investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational study site

The sponsor will inform all investigational study sites about reported relevant events (e.g., SUSARs) according to all applicable regulations. The sponsor will send SUSARs to a study site once ready to enroll and will stop sending SUSARs once the last subject EOT visit for that study site (30 days after last dose) occurs.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the Investigator's Brochure / summary of product characteristics.

9.6.2 Pregnancies

The Investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For all reports, the forms provided are to be used. The Investigator should submit them within the same timelines as an SAE.

9.6.3 Reporting of medical device failures

If required by local regulations, the Investigator must report immediately all failures of non-approved medical devices which could cause health damage, as well as any health damage that may be causally associated with a failure of a non-approved medical device. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.7 Other procedures and variables

Other exploratory variables in this study are resource utilization, assessment of biomarkers and impact of baseline total body weight (TBW) and ideal body weight (IBW) on SSE-FS and AEs. Further details about these exploratory endpoints will be provided in the SAP.

Note: As of Amendment 10, collection of data will be reduced and will focus mainly on acute safety, SSE, and OS. Please see Section 15.6 for further information.

9.7.1 Resource utilization

Information on healthcare resource use that is associated with the management of AEs as well as subject monitoring will be collected by questionnaire (Section 16.8).

9.7.2 Biomarker assessments

Biomarker analyses planned within this study may include predictive, prognostic, and PD biomarkers analyzed from blood or urine. Blood, urine, and tumor biomarker analyses will be dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will have no

scientific value, or there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or does not reach a positive primary endpoint, completion of the biomarker assessments will be based on justification and intended utility of the data. Exploratory biomarker data including CTC analysis will be reported in a separated biomarker report.

9.7.2.1 Urine and blood based biomarker analysis

Blood samples will be obtained from all subjects at the following time points: (1) Cycle 1, Day 1 (Visit 2) and Cycle 4, Day 1 (Visit 8) within 5 days of the visit prior to radium-223 dichloride/placebo administration, and within 5 days of Visit 11 or disease progression, whichever occurs first. Urine samples will be collected at Cycle 1, Day 1, Cycle 4, Day 1, and at Visit 11 or disease progression, whichever occurs first.

- Urine and serum and plasma from blood samples may be evaluated for expression levels of bone-related biomarkers. Elevated levels of bone biomarkers are indicative for e.g., more aggressive disease and are prognostic of worse long-term clinical outcome. In this study, levels of bone biomarkers (measured before, during, and after treatment) that are indicative of bone remodeling (e.g., ALP and bone ALP, procollagen type I N-terminal propeptide) and bone resorption (e.g., urine NTX and I collagen telopeptide [ICTP]/ serum C-terminal telopeptide of type I collagen) may be evaluated and correlated with clinical outcomes (including SSEs, survival, and levels of other biomarkers).

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease and/or about the drug (i.e., mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and/or literature data.

9.7.2.2 Collection of circulating tumor cells for biomarker analyses

Circulating tumor cells (CTCs) are believed to represent a surrogate for tumor cells and can be used as surrogate to demonstrate efficacy of the drug by enumeration of CTCs, but also as source of tumor molecular characterization.

Blood samples will be obtained from all subjects at sites in France, Germany, Israel, Italy, Spain, and the United Kingdom at the following time points: (1) Cycle 1, Day 1 (Visit 2) and every subsequent cycles, Day 1 within 5 days of the visit prior to radium-223 dichloride or placebo administration, and within 5 days of the EOT visit or disease progression, whichever occurs first.

9.7.3 Analysis of the impact of body weight on SSE-FS and AEs

The impact of baseline TBW and IBW on SSE-FS and AEs will be analyzed in this study. Baseline TBW and IBW correspond to the subject's total and ideal body weights on Cycle 1, Day 1 of the study; details will be presented in the SAP.

9.8 Appropriateness of procedures / measurements

The procedures chosen for the evaluation of safety in this study population are consistent with the appropriate and ethical standards used in phase II trials of oncology drugs.

10. Statistical methods and determination of sample size

10.1 General considerations

Subjects will be randomized to radium-223 dichloride/placebo in a 1:1 ratio. 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 PD at time of switch will be counted as one line although 2 different agents have been administered.
- Visceral disease: yes versus no

Statistical analysis will be performed using SAS Institute Inc® (SAS); the version used will be specified in the SAP.

Data from patients who are transferred to the separate extended safety follow-up study may be pooled and analyzed together with the data from this study.

10.2 Analysis sets

The following 2 populations will be analyzed:

ITT: All randomized subjects. The ITT population will be used in the analysis of all efficacy endpoints. Subjects will be included in all ITT analyses according to the treatment to which they are randomized.

Safety: All randomized subjects who have received at least one dose of any study drug. This safety population will be used in the analyses of all safety endpoints. Subjects will be included in the analyses according to the treatment they received.

10.3 Variables and planned statistical analyses

Definition for each variable is given in Section 9.4.

The primary efficacy variable is SSE-FS.

The secondary efficacy variables are specified below:

- OS
- Time to opiate use for cancer pain
- Time to pain progression (only in subjects with baseline WPS ≤8)
- Time to cytotoxic chemotherapy
- rPFS
- Pain improvement rate

Exploratory efficacy variables are:

- Time to first on-study SSE

- Time to bone ALP progression
- Bone ALP response at Week 12 and 4 weeks (± 7 days) after last radium-223 dichloride/placebo dose
- Bone-specific rPFS
- Time to visceral metastases onset (in subjects with no visceral disease at baseline)

10.3.1 Primary efficacy analysis

The overall one-sided type I error rate for the analysis of primary efficacy endpoint SSE-FS is 0.1.

The null hypothesis that both treatment groups have the same SSE-FS distribution will be tested against the alternative hypothesis that the distribution of SSE-FS time in the radium-223 dichloride is different from the placebo group. The test statistic is assumed to be asymptotically normal distribution. SSE free survival will be analyzed using a stratified log-rank test with the same stratification factors as for randomization. The HR (radium-223 dichloride/placebo) will be computed together with the 2-sided 80% and 95% CI using a Cox regression model stratified by the same factors. Kaplan-Meier estimates and survival curves for SSE-FS will also be presented for each treatment groups.

Additional details for the analyses of primary efficacy endpoint will be provided in the SAP.

10.3.2 Secondary efficacy analysis

Secondary efficacy endpoints are specified in Section 9.4.

The secondary efficacy time-to-event endpoints will be analyzed using a stratified log-rank test, with the factors from the randomization used for stratification. A HR with a 2-sided 95% CI from a stratified Cox proportional hazards model will also be provided. Kaplan-Meier estimates and survival curves will also be presented for each treatment group.

Additional details for the analyses of secondary endpoint will be provided in the SAP.

10.3.3 Exploratory efficacy analysis

The exploratory time-to-event efficacy endpoints will be analyzed using a log-rank test, stratified by the same factors as the randomization factors.

Time to visceral metastases onset (in subjects with no visceral disease at baseline) will be analyzed using a log-rank test, stratified by geographical region and previous lines of hormone therapy in metastatic setting, given a sufficient number of subjects with no visceral disease at baseline.

Additional details for the analyses of exploratory endpoint will be provided in the SAP.

10.3.4 Safety analysis

Safety variables will be analyzed using frequency tables and descriptive statistics.

10.4 Determination of sample size

Under the original sample size calculation, sample size is calculated based on the primary endpoint, SSE-FS. EAST 6.3 was used to calculate event number. Assuming a one-sided alpha of 0.1, power of 90%, with a median SSE-FS for the control group of 8.3 months and a randomization ratio of 1:1 between treatments, approximately 160 events will be required to

detect a 50% increase in SSE-FS for a total of 311 subjects in the 2 treatment groups combined. Dropout rate is assumed to be 15%. Dropout was taken into account when calculating the sample size and study duration. The targeted improvement of 50% is not based on a bibliographical reference.

Following the administrative data review (per Amendment 8) conducted on DEC 2017 by a small group of unblinded Sponsor employees, independent of the study team, subject enrollment in this trial was discontinued on APR 2018, prior to accrual of the originally planned sample size.

10.5 Planned interim data review

An administrative interim data review will be performed when a minimum of 80 rPFS events is reached. The interim data review will be primarily focused on the rPFS, and the interim data review results will inform on future radium-223 clinical development plans in this indication. An independent unblinded review committee will be formed.

No formal statistical testing will be performed for either SSE-FS or rPFS at the time of this interim review. Only summary statistics will be produced. There is no plan to stop the trial due to superior efficacy; therefore, no alpha adjustment is applied for this interim look at the primary endpoint of SSE-FS. The study will remain blinded after the interim data review.

Details of the interim data review will be provided in the SAP.

Planned updated analysis

Following primary analysis, at the closure of the study, after the last subject has discontinued treatment and study assessments, an updated analysis will be performed. The updated analysis will be descriptive only and may consist of listings.

11. Data handling and quality assurance

11.1 Data recording

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the study site. The study site must implement processes to ensure this happens. A source document checklist will be used at the study site to identify the source data for all data points collected and the monitor will work with the study site to complete this.

Data recorded from "only screened subjects (screening failures)"

Data of "only screened subjects" will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At a minimum, data to be recorded in the eCRF are demographic information (subject number, date of birth/age, sex, race [if applicable] and ethnicity), the reason for premature discontinuation and date of last visit. These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the CRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

- All information about the SAE

- All information related to the SAE such as:
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the study site prior to the start of the study to review with the study site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the study site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

The data collection tool for this study will be a validated electronic system. Subject data necessary for analysis and reporting will be transmitted into a validated database or data system (e.g., TOSCA; SAS). Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g., IXRS, laboratory, adjudication committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used such as the Medical Dictionary for Regulatory Activities and World Health Organization Drug Dictionary (WHO-DD).

11.4 Missing data

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).

The method used for imputation of missing data will be described in the SAP.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The

Investigator/institution will be informed prior to a sponsor (or designated CRO) audit inspections to ensure all required staff are available during the audit process. The Investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory Health Authority representatives and IEC(s)/IRB(s) are possible. The Investigator should notify the sponsor immediately of any such inspection.

The Investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

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

Subject (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. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The Investigator/institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The Investigator Site file is not to be destroyed without the sponsor's approval.

The contract with the Investigator/institution will contain all regulations relevant for the study site.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms; dose steps; sites]) at any time, which may be due but not limited to the following reasons:

- If the risk-benefit ratio becomes unacceptable owing to, for example,
    - Results of parallel clinical studies
    - Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; dropout 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 site at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC(s)/IRB(s); competent authority(ies); study site; head of study site) must be informed as applicable according to local law.

- All study materials (except documentation that has to remain stored at study site) must be returned to the sponsor or (for radium-223 dichloride samples) be destroyed at the study site in accordance with the local radioprotection regulations. The Investigator will retain all other documents until notification given by the sponsor for destruction.
- 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.
- All ongoing subjects at the time of study termination will finish all study treatments as part of the study.

Details for individual subject's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigators and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the sites will be available in each site's Investigator Site file.

Whenever the term "Investigator" is noted in the protocol text, it may refer to either the Principal Investigator at the study site, or an appropriately qualified, trained and delegated individual of the investigational study site.

The Principal Investigator of each site must sign the protocol signature sheet before subject recruitment may start at the respective site. Likewise, all protocol amendments/integrated protocols must be signed and dated by the Principal Investigator before coming into effect at the respective site.

In addition to signing the protocol signature sheet, all ethical and legal aspects (Section 13) should be in place prior to any subject recruitment.

A complete list of all participating sites and their Investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature page.

13.1.1 Independent data monitoring committee

Not applicable

13.1.2 Independent radiological review

This study will have no central review.

13.1.3 Independent Data Review Committee (IDRC)

An independent unblinded data review committee will be established.

The IDRC will conduct a one-time unblinded review of the data. IDRC review will be supported by an independent unblinded statistical analysis center, as further described in the IDRC operational plan.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each Investigator (including principal and/or any sub Investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 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 sponsor and Investigator abide by 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 sites/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IEC/IRB, head of the study site/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

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 either the sponsor or the Investigator without agreement by both parties. However, the Investigator or the sponsor 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/sponsor 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/sponsor. Any deviations from the protocol must be explained and documented by the Investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and ICF provided by the sponsor or the study site. A sample subject information and ICF is provided as a document separate to this protocol.

Based on this subject information sheet, the Investigator or designee will explain all relevant aspects of the study to each subject or legal representative or proxy consenter (if the subject is under legal protection), prior to her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The Investigator will also inform the subject that written approval of the IRB/IEC has been obtained.

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

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

The signed informed consent statement is to remain in the Investigator Site file or, if locally required, in the subject's note/file of the medical institution.

A summary of the consenting process, participation in the study, and date of informed consent given by the subject should be documented appropriately in the source documentation.

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

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

For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express her own will. Her refusal or the withdrawal of her consent may not be disregarded.

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

A summary of any revised written ICF signed by the subject or a legal representative or a proxy should be appropriately documented by the study site within the source documents.

If at any time during the study the subject would like to withdraw consent, the Investigator must discuss with the subject the active follow-up period without the clinic visits part of the study. If the subject continues to object to having any study data collected the subject must sign the *"Declaration of Objection to the Collection of Study Data after Withdrawal of Consent"* form.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other Investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the Investigator to publish the results upon completion of the study. However, the Investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the Investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the Investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 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.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF. If the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects to be identified.

14. Reference list

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15. Protocol amendments

15.1 Amendment 1

Amendment 1 (dated 16 MAR 2015) is an amendment to the original protocol dated 06 MAY 2014. Changes to the protocol include:

- Clarified the inclusion criterion of menopausal status
- Changed the inclusion/exclusion criteria to permit visceral metastases
- Changed the requirement for baseline scans to be within 3 weeks prior to randomization rather than within 6 weeks of randomization. Increased the screening period from 2 to 3 weeks to allow more time for baseline imaging assessments
- Added an inclusion criterion that subjects must have had progressive disease after treatment with a non-steroidal aromatase inhibitor
- Clarified that all prior SRE-related procedures must be administered prior to randomization
- Clarified that study treatment is radium-223 dichloride/placebo combined with exemestane and everolimus
- Clarified that SSEs should be recorded until the end of active follow-up regardless of whether subjects start new anti-cancer therapies
- Clarified that permanent discontinuation of study treatment is not required for subjects who experience bone or non-bone disease progression unless chemotherapy is required
- Reduced the maximum CTCAE grade required prior to re-dosing with radium-223 dichloride/placebo after recovery from diarrhea, nausea/vomiting, and constipation from Grade ≤2 to Grade ≤1
- Added plasma collection for biomarker analysis
- Added triglycerides, glucose, and phosphate to the list of clinical chemistry tests to be evaluated
- Clarified the timing of blood and urine sample collection for biomarker analysis
- Corrected the calculation of the BPI-SF items from sums to means
- Added a requirement that all relevant symptoms related to SSEs be recorded as AEs
- Replaced the GFR formula with a link to the specific GFR calculator using the MDRD study equation
- Added an exclusion criterion for breast-feeding women
- Replaced bullets with numbering for the lists of inclusion and exclusion criteria
- Removed reference to monitoring of PSA
- Updated information on calculation of sample size, including changing total number of planned subjects from 310 to 311
- Added serum albumin as a laboratory assessment

- Changed the required duration of bisphosphonate treatment from at least 3 months prior to start of study treatment to at least 1 month prior to start of study treatment
- Updated inclusion criteria to include bone lesions asymptomatic
- Updated study design to exclude immediate life-threatening visceral disease and deleted stratum
- Added pulse oximetry O2 saturation >92% to inclusion criteria if lung metastases are present
- Added life-threatening visceral disease, lymphangitic carcinomatosis, ascites requiring paracentesis, and hypersensitivity to the active substance or to any of the excipients of exemestane and everolimus or to other rapamycin derivatives to exclusion criteria
- Changed the timing of evaluation for radiologic progression from 12 weeks to 8 weeks
- Changed the timing of the CT/MRI confirmatory scan from 8 weeks to 6 to 8 weeks
- Updated required interval of coagulation panel testing prior to treatment to ensure within proper safety parameters
- Clarified calculation of determination of sample size per request of the French Ethics Committee
- Removed the inclusion criteria specification that AST and ALT values above the ULN could not be related to liver metastases
- Revised inclusion criteria to allow subjects treated with newly available and other anticoagulants to enter the study
- Added a heading for clarification purposes in dose modifications section
- Specified methods for determining HER2 status in description of screening period to be consistent with the rest of the protocol
- Provided updated information on dosing used in study DC 109
- Updated dose adjustment for everolimus as modifications are applicable based on product label per country
- Moved statement regarding subjects already receiving exemestane and everolimus from inclusion to exclusion criteria
- Added FDG PET scan as an adjunct to CT/MRI in line with RECIST 1.1 guidelines based on feedback from participating sites and regulatory authorities. Guidance was provided to ensure that this additional imaging modality is used for confirmation of new disease only, in compliance with the RECIST 1.1 criteria
- Revised storage conditions for exemestane and everolimus
- Clarified definition of soft tissue lesions
- Updated timing for completion of BPI-SF questionnaire
- Revised exclusion criterion regarding use of biologic response modifiers to be within 4 weeks within randomization

- Updated inclusion criteria requirements for duration of laboratory assessments prior to randomization
- Revised exclusion criterion regarding platelet transfusions to be within 4 weeks prior to randomization
- Added exclusion criteria for known presence of osteonecrosis of jaw
- Clarified that if exemestane or everolimus or further standard of care hormonal anti-cancer therapy are discontinued, radium-223 dichloride/placebo must be discontinued
- Updated requirement for thrombocytopenia to recover to Grade 1 before restarting radium-223 treatment to better ensure patient safety and to align with the dose modification guidance for everolimus

15.1.1 Overview of changes to the study

Modification 1

Clarified the inclusion criterion of menopausal status based on feedback received from the sites

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 2

Changed the inclusion/exclusion criteria to permit visceral metastases based on feedback from the sites

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- 6.2 Exclusion criteria
- 9.4.2.3 Exploratory efficacy endpoints

Modification 3

Changed the requirement for baseline scans to be within 3 weeks prior to randomization rather than within 6 weeks of randomization to ensure the time interval between baseline disease assessment and start of treatment is in line with RECIST 1.1 guidelines. Increased the screening period from 2 to 3 weeks to allow more time for baseline imaging assessments

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- Table 9-1: Schedule of assessments
- 9.2.1 Screening period (Visits 0 to 1)
- 9.2.6 Radiological assessment: tumor and response evaluation

Modification 4

Added an inclusion criterion that subjects must have had progressive disease after treatment with a non-steroidal aromatase inhibitor at the request of the FDA

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion criteria

Modification 5

Clarified that all prior SRE-related procedures must be administered prior to randomization

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion criteria

Modification 6

Clarified that study treatment is radium-223 dichloride/placebo combined with exemestane and everolimus

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- Synopsis: Methodology
- 5.1.1 Study periods and duration
- 6.1 Inclusion criteria
- 7.1 Treatments to be administered
- 7.4.5 Dose administration
- 7.4.6 Dose adjustments, delays, and treatment discontinuations
- 8.1.2 Permitted concomitant therapy
- 8.2 Post-study treatment therapy
- 9.2.3 Treatment period

- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

Modification 7

Clarified that SSEs should be recorded until the end of active follow-up regardless of whether subjects start new anti-cancer therapies

Sections affected include:

- Synopsis: Treatment period
- 5.1.1 Study periods and duration
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.2 Active follow-up without clinic visits
- 9.2.4.3 End of active follow-up

Modification 8

Clarified that permanent discontinuation of study treatment is not required for subjects who experience bone or non-bone disease progression unless chemotherapy is required. This change was made at the request of the FDA.

Sections affected include:

- Synopsis: Methodology
- 6.3.1.1 Withdrawal from treatment period (collection of follow-up data)

Modification 9

Reduced the maximum CTCAE grade required prior to re-dosing with radium-223 dichloride/placebo after recovery from diarrhea, nausea/vomiting, and constipation from Grade ≤2 to Grade ≤1. Fatigue was also added as a toxicity, which required recovery to Grade ≤1 prior to the next study drug administration. These changes were made at the request of the FDA.

Sections affected include:

- 7.4.6 Dose adjustments, delays, and treatment discontinuations

Modification 10

Added plasma to the serum and urine biomarker collection since biomarkers will be assessed from plasma in this study

Sections affected include:

- Table 9-1: Schedule of assessments
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)

- 9.7.2.1 Urine and blood based biomarker analysis

Modification 11

Added triglycerides, glucose, and phosphate to the list of clinical chemistry tests to be evaluated. Glucose and triglycerides need to be monitored per the product labels for everolimus. Phosphate was added to allow a more complete evaluation of Ca+/phosphate metabolism as the subjects will receive concomitant bisphosphonates or denosumab.

Sections affected include:

- Table 9-1: Schedule of assessments
- 9.2.1 Screening period (Visits 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5, and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.3.3 Other baseline characteristics
- 9.6 Safety

Modification 12

Clarified the timing of the blood and urine sample collection for biomarker analysis to ensure consistency

Sections affected include:

- Table 9-1: Schedule of assessments
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.7.2.1 Urine, plasma, and serum based biomarker analysis

Modification 13

Corrected the calculation of the BPI-SF items from sums to means

Sections affected include:

- 9.4.2.2 Secondary efficacy endpoints

Modification 14

Added a requirement that all relevant symptoms related to SSEs be recorded as AEs. Symptomatic skeletal events and the respective CRF (SSE form) requires the Investigator to report the symptoms using a dynamic search list. To be able to select the symptoms in the SSEs form the Investigator must have completed an AE form that reports the relevant symptom(s).

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5 and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.2 Active follow-up without clinic visits
- 9.2.4.3 End of active follow-up
- 9.6.1.3 Assessments and documentation of adverse events

Modification 15

Replaced the GFR formula with a link to the specific GFR calculator using the MDRD study equation. The MDRD formula to be used for the calculation of GFR varies depending on the method used for serum creatinine assessment (standardized/traceable to isotope dilution mass spectrometry method versus non-standardized/non-traceable to isotope dilution mass spectrometry method).

Sections affected include:

- 16.3 Calculation for glomerular filtration rate

Modification 16

Added an exclusion criterion for breast-feeding women

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion criteria
- 6.2 Exclusion criteria

Modification 17

Replaced bullets with numbering for the lists of inclusion and exclusion criteria for consistency with the eCRF

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria
- 6.2 Exclusion criteria

Modification 18

Removed reference to monitoring of PSA because study is being conducted only in women

Sections affected include:

- 9.3.3 Other Baseline Characteristics

Modification 19

Updated information on calculation of sample size, including changing total number of planned subjects from 310 to 311

Sections affected include:

- Synopsis: Number of subjects
- Synopsis: Plan for statistical analysis
- 5.1 Design Overview
- 6. Studying Population
- 10.4 Determination of Sample Size

Modification 20

Added serum albumin >30 g/L as a laboratory assessment

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion Criteria

Modification 21

Changed the required duration of bisphosphonate treatment from at least 3 months prior to start of study treatment to at least 1 month prior to start of study treatment because 1 month is sufficient to allow these treatments to have full effect on the bone function

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion Criteria
- 7.1 Treatments to be administered

- 8.1.2 Permitted Concomitant Therapy

Modification 22

Updated inclusion criteria to include bone lesions asymptomatic

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion Criteria

Modification 23

Updated study design to exclude immediate life-threatening visceral disease and deleted stratum

Sections affected include:

- Synopsis: Study objectives
- 5.1 Design Overview
- Figure 5-1: Study Design Schematic
- 7.3 Treatment Assignment
- 10.1 General Considerations
- 10.3 Variables and statistical analyses
- 10.3.3 Exploratory efficacy analysis

Modification 24

Added pulse oximetry O_2 saturation >92% to inclusion criteria if lung metastases are present

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion Criteria

Modification 25

Added life-threatening visceral disease, lymphangitic carcinomatosis, ascites requiring paracentesis, and hypersensitivity to the active substance or to any of the excipients of exemestane and everolimus or to other rapamycin derivatives to exclusion criteria

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion criteria
- Exclusion Criteria

Modification 26

Changed the timing of the CT/MRI confirmatory scan from 8 weeks to 6 to 8 weeks

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.4.2 Definition of efficacy variables
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modification 27

Changed the timing of evaluation for radiologic progression from 12 weeks to 8 weeks

Sections affected include:

- 5.1.1 Study periods and duration
- Figure 5-1: Study Design Schematic
- 9.1 Tabular Schedule of Evaluations
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.2 Active follow-up without clinic visits
- 9.2.5 End of study
- 9.2.6 Radiological assessment: tumor and response evaluation

Modification 28

Updated required interval of coagulation panel testing prior to treatment to ensure within proper safety parameters

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, and 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)

Modification 29

Clarified calculation of determination of sample size per request of the French Ethics Committee

Sections affected include:

- 10.4 Determination of sample size

Modification 30

Removed the inclusion criteria specification that AST and ALT values above the ULN could not be related to liver metastases

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion criteria

Modification 31

Revised inclusion criteria to allow subjects treated with newly available and other anticoagulants to enter the study

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion criteria

Modification 32

Added a heading for clarification purposes in dose modifications section

Section affected includes:

- 7.4.6 Dose adjustments, delays, and treatment discontinuations

Modification 33

Specified methods for determining HER2 status in description of screening period to be consistent with the rest of the protocol

Section affected includes:

- 9.2.1 Screening period (Visit 0 to 1)

Modification 34

Provided updated information on dosing used in study DC 109

Section affected includes:

- 3.3.1.3 Dosing rationale

Modification 35

Updated dose adjustment for everolimus as modifications are applicable based on product label per country

Section affected includes:

- 7.4.6.1 Radium-223 dichloride dose delays and treatment discontinuations guidance

Modification 36

Moved statement regarding subjects already receiving exemestane and everolimus from inclusion to exclusion criteria

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion criteria
- 6.1 Inclusion Criteria
- 6.2 Exclusion Criteria

Modification 37

Added FDG PET scan as an adjunct to CT/MRI in line with RECIST 1.1 guidelines based on feedback from participating sites and regulatory authorities. Guidance was provided to ensure that this additional imaging modality is used for confirmation of new disease only, in compliance with the RECIST 1.1 criteria

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion Criteria
- 9.1 Tabular schedule of evaluations
- 9.2.1 Screening period (Visit 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.2.6 Radiological assessment: tumor and response evaluation
- Appendix 16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modification 38

Revised storage conditions for exemestane and everolimus

Sections affected include:

- 7.2.1.3 Study treatment with exemestane and everolimus

Modification 39

Clarified definition of soft tissue lesion

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion criteria
- 6.1 Inclusion criteria
- 16.2 Response Evaluation Criteria in Solid Tumors

Modification 40

Updated timing for completion of BPI-SF questionnaire

Sections affected include:

- 9.2.1 Screening period (Visit 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of Active follow-up
- 9.4.2.2 Secondary efficacy endpoints

Modification 41

Revised exclusion criterion regarding use of biologic response modifiers to be within 4 weeks within randomization

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion Criteria
- 6.2 Exclusion criteria
- 8.1.2 Permitted concomitant therapy

Modification 42

Updated inclusion criteria requirements for duration of laboratory assessments prior to randomization

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Inclusion Criteria
- 6.1 Inclusion criteria

Modification 43

Revised exclusion criteria regarding platelet transfusions to be within 4 weeks prior to randomization

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion Criteria
- 6.2 Exclusion criteria
- 8.1.2 Permitted concomitant therapy
- 9.2.3 Treatment Period

Modification 44

Added exclusion criteria for known presence of osteonecrosis of jaw

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion, Exclusion Criteria
- 6.2 Exclusion criteria
- 7.4.6.1 Radium-223 dichloride dose delays and treatment discontinuations guidance

Modification 45

Clarified that if exemestane or everolimus or further standard of care hormonal anti-cancer therapy are discontinued, radium-223 dichloride/placebo must also be discontinued

Sections affected include:

- Synopsis: Methodology
- 5.1.1 Design Overview
- 6.3.1 Withdrawal

Modification 46

Updated requirement for thrombocytopenia to recover to Grade 1 before restarting radium-223 treatment to better ensure patient safety and to align with the dose modification guidance for everolimus

Section affected includes:

- 7.4.61 Radium-223 dichloride dose delays and treatment discontinuations guidance
- 7.4.7 Supportive care guidelines
- 9.2.3 Treatment period

15.1.2 Changes to the protocol text

Changes to the protocol text done in Amendment 1 are provided in Section 15.1.2 of integrated protocol Version 2.0.

15.2 Amendment 3

Amendment 3 (dated 29 JUL 2015) is an amendment to global Amendment 1 of the original protocol dated 16 MAR 2015. Changes to the protocol include:

- Added pain improvement as a secondary endpoint as patients can now be evaluated for pain improvement based on revision of exclusion criteria.
- Changed assessment of bone ALP response from EOT to Week 24.
- Updated the quantification of radium-223 radioactivity in Xofigo® based on the revised primary standardization performed by the US NIST.
- Added text related to counting of SREs for clarification.
- Removed exclusion criteria 13 per objection from participating sites that majority of subjects with advanced breast cancer and bone disease would not be asymptomatic or mildly symptomatic.
- Changed estimated glomerular filtration rate from 60 to 30 to align with denosumab and bisphosphonates labeling and exclude only patients with severe renal impairment.
- Changed thrombocytopenia from Grade 3 to Grade 2 for consistency.
- Removed completion of BPI-SF at screening based on revision of exclusion criteria.
- Changed body weight to be taken within 5 days to allow more time to receive results.
- Changed blood samples to be taken within 5 days to allow more time to receive results.
- Added collection time period for biomarkers to be within 5 days to allow more flexibility.
- Added text for the collection of scans for retrospective analysis.
- Added new Appendix to provide detailed guidance for the administration of the BPI-SF questionnaire.
- Added 8-week time interval for performance of assessments during active follow-up.
- Updated screening procedures for consistency.
- Changed pregnancy test to be taken within 5 days to allow more time to receive results.
- Removed requirement for first dose of study treatment to occur 1 to 3 weeks after randomization.
- Removed requirement that bisphosphonates or denosumab to be administered at least 2 hours before study treatment.
- Modified text for clarification.

- The list of abbreviations was updated to reflect the usage of abbreviations in the amended protocol.

15.2.1 Overview of changes to the study

Modification 1

Added pain improvement as a secondary endpoint as patients can now be evaluated for pain improvement based on revision of exclusion criteria.

Sections affected include:

- Synopsis: Study objectives
- 4. Study objectives
- 5.1.2 Study endpoints
- 9.4.1 Efficacy variables
- 9.4.2.2 Secondary efficacy endpoints
- 10.3 Variables and planned statistical analyses

Modification 2

Changed assessment of bone ALP response from EOT to Week 24. The objective of the biomarker assessment is to evaluate the effect of radium-223 dichloride on the bone markers. The change will allow assessment of bone biomarkers at the end of treatment with radium-223, which corresponds to week 24 rather than at EOT which in this study is intended as the end of treatment of all study medications (radium-223, everolimus and exemestane). In fact exemestane and everolimus treatment may continue beyond week 24 till the subject experiences progression or unacceptable tolerability.

Sections affected include:

- Synopsis: Study objectives
- 4. Study objectives
- 5.1.2 Study endpoints
- 9.4.1 Efficacy variables
- 9.4.2.3 Exploratory efficacy endpoints:
- 10.3 Variables and planned statistical analyses

Modification 3

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 is 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 (52) and current measurements was confirmed and a revised NIST primary reference standard has been issued (53). 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 [53]) 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. A respective variation application and substantial amendment to our CTAs have been initiated. The current standard (NIST 2010 [52]), dial setting and dose **will remain in effect** until a unique implementation date in Q2 2016 as agreed with FDA and EMA. All clinical sites using radium-223 dichloride will be notified in writing about the exact date of implementation prior to the effective date.

Justification for changing the dose to 55 kBq/kg body weight:

A systematic approximately 10% error in the radium-223 NIST standardization (NIST 2010 [52]) means that the current patient dose and the dose documented as safe and efficacious throughout development is 55 kBq/kg body weight and not 50 kBq/kg body weight as declared during clinical trials and in the marketing authorization application / new drug application. However, as this is a systematic error, the actual dose has been the same all the time. In order to keep the actual dose for patients identical to what has been documented and administered so far, also when implementing the new official standard, the nominal value of the patient dose will be changed to 55kBq/kg body weight (NIST update [53]). This change keeps the same accuracy in the nominal value of the dose. Thus, there will be no actual change in the patient dose (amount of radioactivity), it will be only a change in the dose nominal value when corrected according to the new official radium-223 NIST standard. All sites will continue to use the current dial setting (NIST 2010 [52]) for the activity measurements until the implementation date in Q2 2016.

Justification for changing the description of the radioactivity in the vial to 1,100 kBq/mL:

A systematic approximately 10% error in the radium-223 NIST standard (NIST 2010 [52]) means that the Xofigo® solution for injection with a radioactivity concentration claim of 1,000 kBq/mL, which has been tested in pivotal clinical trials and is currently marketed, actually has a concentration of 1,100 kBq/mL. If the drug product concentration is adjusted to 1,100 kBq/mL, the total activity in the vial (6 mL) must be changed from 6,000 kBq/vial to 6,600 kBq/vial (changed from 6.0 MBq/vial to 6.6 MBq/vial in many countries). Xofigo® solution for injection produced according to the new NIST standardization (NIST update [53]), is the same product as before. NOTE: All product received by sites will be labeled with the current standard activity of 1000 kBq/mL until the implementation date in Q2 2016.

Now that the new radium-223 standard has been published, Bayer has applied for labeling and packaging changes, in accordance with the new standards, with each Health Authority for which Bayer holds a marketing application for radium-223 dichloride. Once all approvals have been received, the updated standard will be applied to all active protocols that include

radium-223 dichloride, including this one, and the verification of the patient dose in treatment sites has to be performed using updated dial-settings of dose calibrators.

The change in the NIST radium-223 standard has no impact on subjects; subjects are receiving, and will continue to receive, the same actual dose that was studied in ALSYMPCA 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. Subjects who are on-treatment at the time the new NIST calibration standard goes into effect will be notified of this change and will be required to sign a Patient Information Sheet to acknowledge that they have received information on the updated NIST standard calibration. All subjects randomized after the new calibration standard is in effect will sign a revised ICF that contains the updated NIST standard calibration.

Note: throughout this document the dose of radium-223 dichloride is given as 50 kBq/kg, which is based on the original NIST standardization (NIST 2010 [52]); however, when NIST issues the updated radium-223 dichloride standardization, the dose administered will actually be 55 kBq/kg (based on a change to the reference standard (NIST update [53]) only), though the volume of radium-223 dichloride given to each subject will remain the same.

Sections affected include:

- Synopsis: Dose
- Synopsis: Methodology
- 3.3.1.3 Dosing Rationale
- 5.1.1 Study periods and duration
- 7.1 Treatments to be administered
- 7.2.1.1 Radium-223 dichloride
- 7.4.1 Dose calibration
- 7.4.3 Radium-223 dose calculation
- 14. Reference list

Modification 4

Added text related to counting of SREs for clarification.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 5

Removed exclusion criteria 13 as there was doubt if patient's assessment of pain was a proper definition in being asymptomatic or mildly symptomatic.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 6

Changed estimated glomerular filtration rate from 60 to 30 to exclude patients with severe renal impairment.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 7

Changed thrombocytopenia from Grade 3 to Grade 2 for consistency.

Section affected includes:

- 7.4.6.1 Radium-223 dichloride dose delays and treatment discontinuations guidance

Modification 8

Removed completion of BPI-SF at screening based on revision of exclusion criteria.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.1 Screening period (Visit 0 to 1)

Modification 9

Changed body weight to be taken within 5 days to allow more time to receive results.

Sections affected include:

- 7.4.3 Radium-223 dose calculation
- 9.1 Tabular schedule of evaluations
- 9.2.3 Treatment period
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)

Modification 10

Changed blood samples to be taken within 5 days to allow more time to receive results.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3 Treatment period
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.3 End of active follow-up
- 9.7.2.1 Urine and blood based biomarker analysis

Modification 11

Added collection time period for biomarkers to be within 5 days to allow more flexibility.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)

Modification 12

Added text for the collection of scans for retrospective analysis.

Sections affected include:

- 9.2.6 Radiological assessment: tumor and response evaluation

Modification 13

Added new Appendix to provide detailed guidance for the administration of the BPI-SF questionnaire.

Sections affected include:

- 14. Reference list
- Appendix 16.7 BPI-SF

Modification 14

Added 8-week time interval for performance of assessments during active follow-up.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.4.1 Active follow-up with clinic visits

Modification 15

Updated screening procedures for consistency.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion criteria

Modification 16

Changed pregnancy test to be taken within 5 days of dosing to allow more time to receive results.

Sections affected include:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit

Modification 17

Removed requirement for first dose of study treatment to occur 1 to 3 weeks after randomization as some countries will not be able to meet this requirement. It is not expected that the change will affect the safety of the subjects on study because they will undergo safety laboratory tests and will be assessed for AEs before first administration of radium-223 dichloride to ensure they continue to meet the protocol requirements.

Sections affected include:

- 6. Study population
- 9.1 Tabular schedule of evaluations

Modification 18

Removed requirement that bisphosphonates or denosumab to be administered at least 2 hours before study treatment based on feedback from Clinical Pharmacology that any potential risk for interaction could be excluded. The change is being implemented across the radium-223 clinical program.

Sections affected include:

- 7.1 Treatments to be administered
- 8.1.2 Permitted concomitant therapy

Modification 19

Modified text for clarification.

Sections affected include:

- 6.3.1.1 Withdrawal from treatment period (collection of follow-up data)
- 7.2.1.3 Study treatment with exemestane and everolimus
- 9.1 Tabular schedule of evaluations
- 9.2.4.3 End of active follow-up
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.7.2.1 Urine and blood based biomarker analysis

Modification 20

- The list of abbreviations was updated to reflect the usage of abbreviations in the amended protocol.
- Sections affected include:
- List of abbreviations

15.2.2 Changes to the protocol text

Changes to the protocol text done in Amendment 3 are provided in Section 15.2.2 of integrated protocol Version 3.0.

15.3 Amendment 5

Amendment 5 (dated 28 APR 2016) is an amendment to global Amendment 3 of the original protocol dated 29 JUL 2015. Changes to the protocol include:

- Updated text for estradiol assay as postmenopausal ranges and detection limit for serum/plasma estradiol assay vary per laboratory.
- Updated frequency of bone scans.
- Deleted text for exclusion of bilateral and 2 distinct breast cancers.
- Clarified data collection for pain medication in alignment with completion of the BPI-SF questionnaire.
- Clarified language for everolimus dosing.
- Added text for completion of PRO Questionnaire Information Sheet by study staff for when BPI questionnaire is required to be completed.

- Clarified the process for unblinded staff members to obtain subject's treatment assignment.
- Clarified the drug order process at sites in the USA.
- Clarified radium-223 administration timelines.
- Changed the SRE definition used for eligibility to make it in line with the SRE definition used in prior studies with other bone-targeted agents (Denosumab, bisphosphonates).
- Updated time period for recording of analgesic use in diary.
- Updated text for independent radiological review to include that all digitized images/scans will be collected for retrospective analysis.
- Added text as biomarkers are to be collected before study drug dosing.
- Added PRO Questionnaire Information Sheet for completeness.
- Updated text for clarification.
- Definition of pain progression was revised.
- Added separate collection of opiate use to allow calculation of time to opiate use.
- Removed progression as a separate assessment because progression is assessed radiologically as per tumor assessment schedule.
- Clarified that clinical chemistry assessment will include bone marrow ALP only if that testing can be performed locally.
- Clarified timing of technetium-99m bone scans and CT scans.
- Updated study medical expert and contact information
- Added sampling for CTCs, which are believed to represent a surrogate for tumor cells and can be used as a surrogate to demonstrate efficacy of the drug by enumeration of CTCs but also as a source of tumor molecular characterizations.

15.3.1 Overview of changes to the study

Modification 1

Updated text for estradiol assay as postmenopausal ranges and detection limit for serum/plasma estradiol assay vary per laboratory.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion Criteria.

Modification 2

Updated frequency of bone scans. All bone lesions identified at baseline by bone scan need to be scanned by CT or MRI and progression in bone needs to be confirmed by CT/MRI. The CT or MRI scans are to be performed at an interval of every 8 weeks (± 7 days). Under these

circumstances, a bone scan interval of 12 weeks, instead of 8 weeks, is appropriate and is more in line with standard clinical practice resulting also in a lower radiation exposure of patients.

Section affected includes:

- 9.2.6 Radiological assessment: tumor and response evaluation.

Modification 3

Deleted text for exclusion of bilateral and 2 distinct breast cancers. Eligible patients for this study must have stage IV (Any T, Any N, M1) metastatic disease and be considered candidates for second or further line of therapy. None of the recent studies (i.e. BOLERO, PALOMA) in metastatic setting excluded patients with such conditions.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion Criteria.

Modification 4

Clarified data collection for pain medication in alignment with completion of the BPI-SF questionnaire.

Sections affected include:

- 8.1.2 Permitted concomitant therapy
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up.

Modification 5

Clarified language for everolimus dosing. Following input from Investigators, start of everolimus at a dose of 5 mg/day is an approach that may be used in some patients as per their institutional standard practice. The language in the protocol has been clarified mentioning that the dose of 10 mg/day is actually the recommended dose and that the starting dose should be in line with the local label and/or local standard of practice.

Sections affected include:

- 7.1 Treatments to be administered
- 7.2.1.3 Study treatment with exemestane and everolimus
- 7.4.5 Dose administration

- 7.4.7 Supportive care guidelines
- 8.1.2 Permitted concomitant therapy
- 9.2.3 Treatment period.

Modification 6

Added text for completion of PRO Questionnaire Information Sheet by study staff for when BPI questionnaire is required to be completed.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up.

Modification 7

Clarified the process for unblinded staff members to obtain subject's treatment assignment.

Section affected includes:

- 7.3 Treatment assignment.

Modification 8

Clarified the drug order process at sites in the USA.

Section affected includes:

- 7.3 Treatment assignment.

Modification 9

Clarified radium-223 administration timelines.

Section affected includes:

- 7.2.1.1 Radium-223 dichloride.

Modification 10

Changed the SRE definition used for eligibility to make it in line with the SRE definition used in prior studies with other bone-targeted agents (Denosumab, bisphosphonates).

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.1 Inclusion Criteria.

Modification 11

Updated time period for recording of analgesic use in diary.

Section affected includes:

- 9.1 Tabular schedule of evaluations.

Modification 12

Updated text for independent radiological review to include that all digitized images/scans will be collected for retrospective analysis.

Section affected includes:

- 13.1.2 Independent radiological review.

Modification 13

Added text as biomarkers are to be collected before study drug dosing.

Section affected includes:

- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit).

Modification 14

Added PRO Questionnaire Information Sheet for completeness.

Sections affected include:

- 16.9 Patient Reported Questionnaire Information Sheet

Modification 15

Updated text for clarification.

Sections affected include:

- Synopsis: Study objectives
- 4. Study objectives
- 5.1.2 Study endpoints
- 6. Study Population
- 9.1 Tabular schedule of evaluations
- 9.4.1 Efficacy variables
- 9.4.2.2 Secondary efficacy endpoints

- 9.4.2.3 Exploratory efficacy endpoints
- 9.6.1.3 Assessments and documentation of adverse events
- 9.7.2 Biomarker assessments
- 10.3 Variables and planned statistical analyses

Modification 16

Definition of pain progression was revised.

Sections affected include:

- List of abbreviations
- 9.4.2.2 Secondary efficacy endpoints.

Modification 17

Added separate collection of opiate use to allow calculation of time to opiate use.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up.

Modification 18

Removed progression as a separate assessment because progression is assessed radiologically as per tumor assessment schedule.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5 and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up.

Modification 19

Clarified that clinical chemistry assessment will include bone marrow ALP only if that testing can be performed locally.

Sections affected include:

- Section 9.1 Tabular schedule of evaluations
- 9.2.1 Screening period (Visit 0 to 1)
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.2 Visits 3, 5 and 7 (Day 15 of Cycles 1, 2, and 3 ±3 days at each visit) and unscheduled visits
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up.
- 9.3.3 Other baseline characteristics

Modification 20

Clarified timing of technetium-99m bone scans and CT scans.

Sections affected include:

- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.3 Ongoing treatment with exemestane and everolimus (Visits 11, 12 and onwards)
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.3 End of active follow-up
- 9.2.6 Radiological assessment: tumor and response evaluation

Modification 21

Updated study medical expert and contact information.

Section affected includes:

- Title page

Modification 22

Added sampling for CTCs. CTCs are believed to represent a surrogate for tumor cells and can be used as a surrogate to demonstrate efficacy of the drug by enumeration of CTCs but also as a source of tumor molecular characterizations.

Sections affected include:

- List of Abbreviations
- 9.1 Tabular schedule of evaluations
- 9.2.3.1 Visits 2, 4, 6, 8, 9, 10 (Day 1 of Cycles 1 through 6 ±7 days at each visit)
- 9.2.3.4 End of treatment visit
- 9.7.2.2 Collection of Circulating Tumor Cells for Biomarker Analyses

15.3.2 Changes to the protocol text

Changes to the protocol text done in Amendment 5 are provided in Section 15.3.2 of integrated protocol Version 4.0.

15.4 Amendment 8

Amendment 8 (dated 18 MAY 2017) is an amendment to global Amendment 5 of the original protocol dated 09 JUL 2015. Changes to the protocol include:

- Removed timeframe for prior chemotherapy administered for adjuvant/neo-adjuvant disease.
- Added text to provide tolerance limits for permitted radiation.
- Text was updated to provide clarity to study sites.
- Text was added for consistency with Table 9-1: Schedule of assessments.
- Text was added as it is mandatory to include for studies involving Japanese centers where the CSP requires the use of medical devices that are currently non-approved in Japan.
- Clarified sites at which CTCs are collected.
- Added interim data review.
- Updated company name.
- Updated text for independent radiological review.
- Added text for the establishment of an independent unblinded data review committee.
- Reformatted page for signature of the sponsor’s medically responsible person.

15.4.1 Overview of changes to the study

Modification 1

Removed timeframe for prior chemotherapy administered for adjuvant/neo-adjuvant disease. More recent data from chemotherapy combination studies with Xofigo shows good safety profile of the combination. In addition, long term safety follow-up data from ALSYMPCA

showed good safety profile for patients that received subsequent chemotherapy. At the time of the current study set up, this data was not available.

Sections affected include:

- Synopsis: Diagnosis and main criteria for inclusion and exclusion
- 6.2 Exclusion criteria.

Modification 2

Added text to provide tolerance limits for permitted radiation.

Sections affected include:

- 7.4.4 Study drug dose preparation.

Modification 3

Text was updated to provide clarity to study sites.

Sections affected include:

- 9.1 Tabular schedule of evaluations.

Modification 4

Text was added for consistency with Table 9-1: Schedule of assessments. Although monthly visits might not be possible for some patients, tumor assessments as per time schedule described in Section 9.2.6 might be feasible and will allow collection of data for disease response assessment related to some efficacy endpoints (radiological PFS, radiological bone-specific PFS, etc).

Sections affected include:

- 9.2.4.2 Active follow-up without clinic visits.

Modification 5

Text was added as it is mandatory to include for studies involving Japanese centers where the CSP requires the use of medical devices that are currently non-approved in Japan.

Sections affected include:

- 9.6.3 Reporting of medical device failures.

Modification 6

Clarified sites at which CTCs are collected.

Sections affected include:

- 9.7.2.2 Collection of circulating tumor cells for biomarker analyses.

Modification 7

Added interim data review.

Sections affected include:

- 10.5 Planned interim data review.

Modification 8

Updated company name. Bayer HealthCare AG merged with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer HealthCare AG ceased to exist and Bayer AG became its legal successor and automatically took over all of the Bayer HealthCare AG's rights, obligations and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor.

Sections affected include:

- Header
- Title page

Modification 9

Updated text for independent radiological review.

Sections affected include:

- 9.2.6 Radiological assessment: tumor and response evaluation
- 13.1.2 Independent radiological review

Modification 10

Added text for the establishment of an independent unblinded data review committee.

Sections affected include:

- List of abbreviations
- 13.1.3 Independent Data Review Committee

Modification 11

Added text for the establishment of an independent unblinded data review committee.

Section affected includes:

- Signature of the sponsor's medically responsible person

15.4.2 Changes to the protocol text

Changes to the protocol text done in Amendment 8 are provided in Section 15.4.2 of integrated protocol Version 5.0.

15.5 Amendment 9

Amendment 9 (dated 03 APR 2018) is an amendment to Version 5.0 of the protocol, dated 23 MAY 2017. Changes to the integrated protocol include:

- New request that bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of the investigator's causality assessment.
- Addition of possibility to transition to long-term follow-up study for subjects who have completed at a minimum the end of treatment visit or 30 days from last study treatment dose, whichever is latest
- Updated sponsor's medically responsible person
- Clarification to AE and SAE reporting requirements during active follow-up in the Schedule of Assessments
- Minor clarifications

15.5.1 Overview of changes

15.5.1.1 Modification 1

Bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long-term follow-up, regardless of the investigator's causality assessment.

Sections affected include:

- Synopsis
- 5.1.1 Study periods and duration
- 9.1 Tabular schedule of evaluations
- 9.2.3.4 End of treatment visit
- 9.2.4.1 Active follow-up with clinic visits
- 9.2.4.2 Active follow-up without clinic visits
- 9.2.4.3 End of active follow-up
- 9.6.1.3 Assessments and documentation of adverse events
- 9.6.1.4 Reporting of serious adverse events

Rationale:

The ERA 223 study, a phase III randomized trial in prostate cancer patients examining radium-223 dichloride versus placebo in combination with abiraterone and prednisone (study number 15396, NCT02043678) was unblinded based on the IDMC recommendation following an ad hoc independent analysis where more treatment-emergent fractures, SSE-FS, and total deaths events were observed in the active treatment arm compared with the placebo arm. Based on these data European Health Authorities requested that all bone fractures and bone associated events (e.g., osteoporosis) occurring during study and in the follow-up period should be documented regardless of the investigator's causality assessment.

15.5.1.2 Modification 2

Clarification of transition to long-term extension study to allow collection of long term safety data

Sections affected include:

- Synopsis
- 5.1.1 Study periods and duration
- 5.3 End of study
- 9.2.5 End of study

Rationale

To allow collection of long term safety data, subjects who have completed at a minimum the end of treatment visit or 30 days from last study treatment dose, whichever is latest, may be transitioned into a separate long-term follow-up study. Until the transition to the long-term follow-up study, subjects will continue to follow all the protocols required procedures and visits in the current protocol.

15.5.1.3 Modification 3

The sponsor's medically responsible person has changed and signature page was updated to reflect this.

Sections affected include:

- Signature of the sponsor's medically responsible person

15.5.1.4 Modification 4

Clarification of footnotes in the schedule of assessment to reflect consistency with the body text. The AEs and SAEs reporting requirements during active follow-up apply regardless of whether the patient has clinic visits or not. The footnotes previously indicated these reporting requirements applied only in the case without clinic visits, which is inconsistent with the active follow up description in Section 9.2.4.1.

Sections affected include:

- 9.1 Tabular schedule of evaluations

15.5.1.5 Minor clarifications

For Word-related technical reasons, numbered footnotes have been replaced with a summary of changes at the start of each amended section.

15.5.2 Changes to the protocol text

Changes to the protocol text are provided in a separate tracked changes document.

15.6 Amendment 10

Amendment 10 (Version 7.0), dated 04 DEC 2019, is a global amendment to Version 6.0 of the integrated protocol.

15.6.1 Overview of changes

Overall rationale for the amendment

At the time of the primary analysis, only a limited number of subjects were receiving study medication (exemestane and everolimus).

After implementation of **CSP Amendment 9**, subjects who completed the EOT visit could be transferred to a separate extended safety follow-up study for their remaining follow-up. After implementation of **CSP Amendment 10,** all such subjects will be transferred; only subjects on oral treatment will remain on study, and no post-treatment data will be collected beyond the 30-day safety follow-up (EOT visit).

As the key efficacy objectives will have been accomplished, long-term safety transferred, and only a limited number of subjects will remain in this study, in order to reduce the burden to study subjects, collection of data will be reduced and will focus mainly on **acute safety, SSE, and OS**. Accordingly, the updated analysis following the closure of the study will be descriptive only and may consist of listings. Once subjects are rolled over, the long-term safety will be collected and assessed entirely in the separate extended safety follow-up study.

High-level descriptions and rationales of the changes and the affected sections are listed below.

Sections	Description of change	Rationale
Synopsis 4. Study objectives 5.1.1 Study periods and duration 5.1.2 Study endpoints 9.4.1 Efficacy variables 9.6 Safety 9.7 Other procedures and variables	Collection of data will be reduced to focus on acute safety, SSE and OS. Clarified the assessment of safety endpoints.	Due to the limited number of patients beyond primary analysis and to reduce the burden to study subjects, collection of data will be reduced and will focus mainly on acute safety, SSE, and OS.
Synopsis 5.1.1 Study periods and duration 9.1 Tabular schedule of evaluations 9.2.3.2 Visits 3, 5 and 7 […] 9.2.3.3 Ongoing treatment with exemestane and everolimus […] 9.2.3.4 End of treatment visit 9.2.4 Active follow-up 9.2.6 Radiological assessment: tumor and response evaluation 9.6 Safety	Updated schedule of assessments and procedures	To reduce the burden to study subjects, the schedule of assessments and procedures were modified. Updated frequency of visits to every 8 weeks and imaging according to local standard practice, until disease progression or treatment discontinuation. Pain, QoL assessments and biomarker collection are being discontinued as they will no longer be analyzed. Laboratory assessments were reduced to monitoring of adverse events of study drugs. ECGs will be performed according to local standard practice.

Sections	Description of change	Rationale
Synopsis 5.1.1 Study periods and duration 5.3 End of study 6.3.1 Withdrawal 6.3.1.1 Withdrawal from treatment period […] 8.2 Post-study treatment therapy 9.1 Tabular schedule of evaluations 9.2.3.3 Ongoing treatment with exemestane and everolimus […] 9.2.4 Active follow-up 9.2.3.4 End of treatment visit 9.2.5 End of study 10.4 Determination of sample size	Clarification on the sample size Updated criteria to transition subjects to separate extended safety follow-up study Removal of active follow-up periods	Subject enrollment in this trial was discontinued in APR 2018, prior to accrual of the originally planned sample size. By the time of primary analysis, all patients in follow-up will be transitioned to the separate extended safety follow-up study (16996). After primary analysis, subjects discontinuing study treatment will be directly transitioned to the separate extended safety follow-up study (16996). Therefore, the active follow-up periods are no longer applicable.
Synopsis 5.1.1 Study periods and duration 6.3.1.1 Withdrawal from treatment period […] 7.1 Treatments to be administered 7.4.6.1 Radium-223 dichloride dose delays […] 9.2.3 Treatment period 9.2.3.3 Ongoing treatment with exemestane and everolimus […]	Updated criteria for discontinuation of study drugs	A clarification in regards to the criteria for the discontinuation of the study drugs was included to make it aligned with standard clinical practice, i.e., subjects presenting disease progression (defined as as radiological progression, either by RECIST or bone progression, clinical progression), initiation of new anti-cancer therapy, occurrence of unacceptable toxicity or discontinuation of treatment for other reasons will prompt discontinuation of study drugs.
Synopsis 5.1.1 Study periods and duration 5.3 End of study 9.2.5 End of study	Updated end of study criteria	The definition of EOS was modified to reflect the changes in study status. EOS will occur at the time the last subject on treatment discontinues oral exemestane and/or everolimus treatment and completes end of treatment visit or discontinues from this study for another reason. In addition, guidance on reporting of safety-related events after primary analysis for sites/subjects not transitioning to extended safety follow-up study was included.
Synopsis 7.5 Blinding 10.5 Planned interim data review	Clarification on the blinding of the study and on the analysis performed after last subject last visit.	Following the primary analysis, the study will be fully unblinded. After the last subject has discontinued treatment and study assessments, an updated analysis will be performed.

Sections	Description of change	Rationale
10.1 General considerations	Clarification on the further analysis of data from patients who were transferred	Data from patients who are transferred to the separate extended safety follow-up study may be pooled and analyzed together with the data from this study.
10.3.2 Secondary efficacy analysis	Removal of 80% CI from the secondary efficacy time-to-event endpoints.	Per Sponsor decision, there is no need to report 2 different confidence intervals for every endpoint in a study that is being terminated. The 95% CI was retained as it is the most commonly used CI in the literature. Of note, both CIs will be retained for the primary endpoint. The 80% value corresponds to the 10% 1-sided hypothesis test (equivalent to 20% 2-sided) used as the basis of study power.
Title page Signature of the sponsor's medically responsible person	Sponsor's medical expert and sponsor's medically responsible person were changed. Role of signatory was changed.	Administrative change.
15. Protocol amendments and 15.1.2, 15.2.2, 15.3.2 and 15.4.2 Changes to the protocol text Throughout	The detailed old vs. new text comparisons for protocol amendments 1, 3, 5, and 8, and descriptions on how those comparisons were detailed, were replaced with a reference to the respective protocol amendment. Old annotations from previous amendments were removed.	To improve readability, and to reduce complexity of the protocol.

15.6.2 Changes to the protocol text

Changes to the protocol text are provided in a separate tracked-changes version.

16. Appendices

16.1 National Cancer Institute-Common Terminology Criteria, version 4.03

This study will utilize the NCI-CTCAE v4.03 for toxicity and SAE reporting. A copy of the CTCAE v4.03 can be downloaded from the website: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. All appropriate treatment areas should have access to a copy of the CTCAE v4.03.

16.2 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Disease response and progression will be evaluated in this study using a modified version of RECIST version 1.1.(51) The modification refers to bone lesions assessment: all bone lesions are considered non-measurable and new bone lesions identified by bone scan will need to be confirmed by further imaging (CT/MRI).

Definitions:

Bone lesions: malignant findings in skeleton.

Soft tissue lesions: Malignant finding in soft tissue: skin, subcutaneous, muscle, fat, lymph nodes.

Visceral lesions: Malignant finding in visceral organs: lung, liver, brain, etc.

Measurable lesions: Lesions that, at baseline, meet the requirements for being reproducibly quantifiable (see section below for detailed definition of measurable lesions).

Non-measurable lesions: Lesions that, at baseline, do not meet the below-described requirements. These lesions cannot be chosen for quantitative assessment, and must be assessed qualitatively only.

Target lesions: Lesions that are chosen at baseline (from the set of measurable lesions) for quantitative assessment throughout the trial, using rules outlined below. A lesion that has been selected as a target lesion remains a target lesion for the rest of the trial.

Non-target lesions: Lesions that are not chosen at baseline for quantitative assessment, and must be assessed qualitatively throughout the trial. A lesion that has been selected as a non-target lesion remains a non-target lesion for the rest of the trial.

Methods of Measurement:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

All measurements must be recorded in millimeters (or decimal fractions of centimeters).

For measurements of tumors other than lymph nodes, the longest unbroken diameter seen on an axial slice is recorded.

Lymph nodes must always be measured in the short axis (the longest measurement on an axial slice perpendicular to the longest diameter of the lymph node). Lymph nodes less than 10 mm in short axis diameter are defined as normal.

CT/MRI of chest/abdomen/pelvis and any additional sites of disease (if clinically indicated) will be performed for all patients.

In addition, all patients will have their bone disease assessed by technetium-99m bone scan with careful identification of all disease-related hotspots.

If FDG PET/CT or FDG PET scan is performed as part of the standard of practice imaging, the results of the FDG PET scan can be used as a complement to CT scanning in the assessment of disease progression – based on occurrence of new lesions – as per the RECIST 1.1 algorithm (See section on New lesions in this appendix).

The CT component of the FDG PET/CT scan, as per RECIST 1.1, can be used for tumor measurements only if the site can document that the CT performed as part of a FDG PET/CT scan is of identical diagnostic quality to a diagnostic CT.

FDG PET/CT or ^{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.

Clinical lesions might be assessed clinically only as per the following rules: clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and ≥10mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Baseline Assessment:

Identifying measurable disease:

Non-nodal malignant lesions: Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thickness greater than 5mm are used, the minimum size should be twice the slice thickness.
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant lymph nodes: To be considered pathologically enlarged, a lymph node must be ≥ 10 mm in short axis when assessed by CT scan. To be considered measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.

Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Identifying non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with short axis 10-14 mm) are considered non-measurable disease.

Bone lesions:

All bone lesions (blastic, lytic, mixed type) will be considered non-measurable lesions.

Selection of target and non-target lesions:

At baseline, lesions are divided into those that will be followed quantitatively (target lesions) and those that will be followed qualitatively (non-target lesions).

Target lesions:

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. These lesions should be selected on the basis of their size (lesion with the longest diameter/short axis for lymph nodes), be representative of all involved organs and should be suitable for reproducible repeated measurements.

For the purposes of this selection, all lymph nodes should be regarded as a single organ. If there are multiple chains/regions, consider selecting one from each.

The sum of the diameters (longest diameter for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated by adding all target lesion diameters/short axis (for lymph nodes) and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference measurement when looking for evidence of objective response at later visits.

If there are more than 5 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions.

Non-target lesions:

Non-target lesions include all non-measurable lesions, plus any measurable lesions over and above the maximum 5 listed as target lesions.

Bone lesions are considered non-measurable and therefore should all be classified as non-target lesions.

Post-baseline assessment:

At every response assessment visit after baseline, the Investigator will assess the following:

- target lesions selected at baseline, and
- non-target lesions selected at baseline, and
- search for new lesions.

The lesion assessments are then combined into an assessment of the entire subject at that visit (called the visit response or the overall response).

Target lesion assessment:

The Investigator will measure each target lesion in the same manner as at baseline.

Malignant lymph nodes will be measured in short axis diameter.

If a lesion decreases in size to the point where it is still present, but cannot be measured accurately, a default value of 5 mm should be recorded for its diameter.

If a lesion has disappeared, a value of 0 mm should be recorded for its diameter.

If a lesion has split into distinct fragments, the longest diameter of each fragment should be measured, and the diameters added together.

If 2 lesions have merged, the longest diameter of the entire resulting lesion should be measured.

The sum of diameters will be calculated by adding all target lesion diameters/short axis (for lymph nodes).

The sum of diameters is always compared to 2 reference points: the baseline sum of diameters, and the smallest sum of diameters seen during the trial (also called the nadir). The baseline may actually be the nadir, if there has been no reduction in the sum of diameters during the trial. The target lesion response is then classified as follows in Table 16–1.

Table 16–1: Target lesion response

Response	Response characteristics
Complete response (CR)	Complete disappearance of target lesions All target lymph nodes <10 mm
Partial response (PR)	At least a **30% decrease** in the sum of diameters from baseline
Progressive disease (PD)	At least a **20% increase** in the sum of diameters from the smallest value seen during the trial (including baseline), with at least a **5 mm** absolute increase in the sum
Stable disease (SD)	Neither enough shrinkage to qualify as PR, nor enough growth to qualify as PD
Non-evaluable (NE)	One or more target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

Please note that when lymph nodes are included as target lesions, a CR may occur even when the sum of diameters is not zero, since a normal lymph node will have a diameter greater than zero but less than 10 mm.

Non-target lesion assessment:

Non-target lesions are assessed as a whole. After examining each non-target lesion, the Investigator will classify the non-target lesion response as follows in Table 16–2.

Table 16–2: Non-target lesion response

Response	Response characteristics
Complete response (CR)	Complete disappearance of all non-target lesions All non-target lymph nodes <10 mm
Progressive disease (PD)	Unequivocal progression of non-target lesions as a whole. • Subjective call by expert reviewer • Evaluated as a group, not lesion by lesion
Non-CR/Non-PD	Non-target lesions still present, without unequivocal progression
Non-evaluable (NE)	One or more non-target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

To achieve unequivocal progression in patients with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression.

New lesions:

Any new lesion that is considered unequivocally malignant is evidence of progression, with no minimum size requirement.

An individual radiological event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing. This means that if a new lesion is not unequivocal at the time of initial detection, but later becomes unequivocal, the date of progression will be the date it was first detected.

Specific considerations for new bone lesions and for unequivocal progression of existing bone lesions:

The finding of a new bone lesion or progression of existing bone lesions should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor: some new bone lesions or unequivocal increase in size of existing lesions may be simply healing or flare of pre-existing lesions.

The following rules will apply:

- A new bone lesion or progression of existing bone lesion/s initially identified on a Tc99m bone scan must be confirmed by CT or MRI. If confirmed by CT/MRI, the date of occurrence of the new lesion or of progression of existing bone lesion/s will be the date it was initially detected (by Tc99m bone scan) even if the confirmation by CT/MRI was done at a subsequent scan.
- A new bone lesion or progression of existing bone lesions initially identified by CT/MRI (and not visible on a Tc99m bone scan) will not need further confirmation by CT/MRI unless not considered unequivocal at time of initial documentation. The date of occurrence of new lesion or progression of existing lesions will be the date it was initially detected by CT/MRI.

New lesions and FDG PET imaging

New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

- (-) FDG PET at baseline and (+) FDG PET at follow-up = Progressive Disease (PD) based on a new lesion
- No FDG PET at baseline and (+) FDG PET at follow-up = PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of PD is the date of the initial FDG PET scan.
- No FDG PET at baseline and (+) FDG PET at follow-up corresponding to a pre-existing lesion on CT that is not progressing is **not** PD

Note: A ‘positive’ FDG PET scan lesion means one with uptake greater than twice that of the surrounding tissue on the attenuation corrected image

Visit response:

The response of the target lesions, the response of the non-target lesions, and the presence or absence of new lesions are combined into the visit response for the entire subject at this visit, using the tables below.

Table 16–3: Visit Response: Patients with target lesions (with or without non-target lesions)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

The following text descriptions of the visit response are logically equivalent to the tables above.

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions from the smallest sum on-study (this includes the baseline sum if that is the smallest on-study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions also constitutes progressive disease. Ascites or pleural effusion will be recorded as disease progression only if proven malignant.

In the absence of target disease, the following will apply (Table 16–4).

Table 16–4: Time Point Response: Patients with non-target lesions only

Non-Target Lesions	New Lesions[a]	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [b]
Not all evaluated	No	NE
Unequivocal PD[c]	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.
[a] New lesions must be unequivocal (see bone lesions specifications).
[b] "Non-CR/non-PD" is preferred over "stable disease".
[c] "Unequivocal PD": Subjective call by expert reviewer. Evaluated as a group, not lesion by lesion

16.3 Calculation for glomular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated glomerular filtration rate (GFR), calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula can be found at the following web site: http://www.kidney.org/professionals/kdoqi/gfr_calculator.

16.4 New York Heart Association Functional Classification

Class	NYHA Functional Classification
I	Subjects have cardiac disease but *without* the resulting *limitations* of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

16.5 ECOG performance status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

16.6 Interaction of everolimus with other medicinal products

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and P-glycoprotein are listed in Table 16–5 below.

Table 16–5: Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)	Recommendations concerning co-administration
Potent CYP3A4/P-glycoprotein inhibitors		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C_{max} ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of everolimus and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	None
Telithromycin, clarithromycin	Not studied. Large increase in everolimus concentration is expected.	None
Nefazodone	Not studied. Large increase in everolimus concentration is expected.	None
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir	Not studied. Large increase in everolimus concentration is expected.	None
***Moderate* CYP3A4/PgP inhibitors**		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C_{max} ↑2.0-fold (range 0.9-3.5)	Use caution when co-administration of moderate CYP3A4 inhibitors or P-gp inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or P-gp inhibitor, dose reduction to 5 mg daily or 5 mg every other day may be considered. However, there are

Table 16–5: Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)	Recommendations concerning co-administration
		no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended.
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C_{max} ↑2.3-fold (range1.3-3.8)	None
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C_{max} ↑1.8-fold (range 1.3-2.6)	None
Fluconazole	Not studied. Increased exposure expected.	None
Diltiazem	Not studied. Increased exposure expected.	None
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	None
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
Potent CYP3A4 inducers		
Rifampicin	AUC ↓63% (range 0-80%) C_{max} ↓58% (range 10-70%)	Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments applied on Day 4 and 8 following start of the inducer. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the co-administration.

Table 16–5: Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)	Recommendations concerning co-administration
Corticosteroids (e.g., dexamethasone, prednisone, prednisolone)	Not studied. Decreased exposure expected.	None
Carbamazepine, phenobarbital, phenytoin	Not studied. Decreased exposure expected.	None
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	None
St John's Wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; CYP = cytochrome P_{450}; P-gp = P-glycoprotein.

16.7 BPI-SF

The severity of pain and its impact on daily functions will be self-assessed by the study subjects using the BPI-SF (54) measure.

The BPI-SF allows subjects to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function (e.g., general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). The BPI-SF is an 11-item, self-administered, clinically valid, reliable, and responsive measure developed to assess pain related to cancer. The instrument is available in validated multilingual versions; on average, it requires less than 10 minutes to complete the questionnaire.

All BPI items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 (no pain) to 10 (pain as bad as you can imagine) numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales. It has a 24-hour recall period.

The BPI-SF will be self-administered by the subject at Dose 1, Day 1 (before the start of study treatment), at each treatment visit, at the end of treatment visit and follow-up clinic visits. At the beginning of each scheduled visit, before meeting with the Investigator, subjects will be asked to complete the BPI-SF, with the exception of Question 2 (locating areas of pain on a diagram) and Question 7 (regarding use of pain medication). Subjects will not be asked to answer Question 2 because the information will not be used for the score. Subjects will not be asked to answer Question 7 because pain medication used is captured elsewhere in the eCRF. The items are aggregated into 2 dimensions: (1) *Pain Severity Index*, using the sum of the 4 items on pain intensity and (2) *Function Interference Index*, using the sum of the 7 pain interference items. The *Function Interference Index* is scored as the mean of the item scores multiplied by 7, given that more than 50% (or 4 of 7), of the items have been completed.

The BPI-SF should be self-administered by the subject alone during her scheduled visit at the site. The instrument should be administered at the start of the visit, before the subject sees the physician so that any interaction between the subject and physician will not influence the

subject's responses to the questionnaire. The questionnaire should also be administered before the subject is asked about AEs and concurrent illnesses, again so that any discussions of health problems do not influence the subject's responses.

A quiet place should be provided for the subject to complete the BPI-SF. It is important that the subject completes the BPI-SF alone, without any advice from family members or friends who may accompany her.

How should the Questionnaire be introduced?

A sample script for introducing the questionnaire is given below.

"Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, we will ask you to complete this questionnaire about your health on the day of each clinic visit. Remember that this is not a test and there are no right or wrong answers. Choose the answer that best describes the way you feel. I will quickly review the questionnaire when you are done to make sure that all the questions have been answered. You should answer these questions by yourself. Your spouse or other family members should not help you when you answer the questionnaire. I will be nearby in case you want to ask me any questions. Please let me know when you have finished the questionnaire."

What to do if the subject asks for clarification?

Some subjects may ask the meaning of specific questions. If this happens, the staff member can assist the subject by re-reading the question for them verbatim. If the subject asks what something means, do not try to explain what the question means, but tactfully suggest that the subject use her own interpretation of the question. All subjects should answer the questions based on what they think the questions mean, or the study results may be biased.

Questionnaire completion and review of worst pain score over the previous 7 days

At the beginning of each visit, please check that the subject has completed the questionnaire, check that all of the questions have been answered. If the questionnaire is not complete, point out to the subject that some of the questions were not answered. If the subject does not quickly volunteer to answer these items, ask her whether she had any difficulty completing the questionnaire. If the subject says that she had trouble understanding a question, ask her why she had difficulty with that item. Re-read the question for her verbatim, but do not attempt to explain or reword the question, as explained before. If the subject is still unable to answer the question, accept the questionnaire as is.

Some subjects may be confused by the response choices. They may want to respond with "I don't know" or some other response choice that is not available. If this happens, try to help the subject choose one of the response categories by saying something like: "I know that it may be difficult for you to choose an answer, but which of these answers do you think comes closest to the way that you are thinking or feeling?" If the subject still cannot select an answer, accept the questionnaire as is.

Occasionally, subjects may not report having difficulty with a question or the response choices, but still may hesitate or refuse to answer an item or items. If this happens, accept the questionnaire as is.

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BRIEF PAIN INVENTORY (SHORT FORM)

Date of assessment _ _ | _ _ | 2 0 _ _
day month year

Time of assessment _ _ : _ _
hours minutes (00:00 - 23:59)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

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

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

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

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

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

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

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

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

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

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9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

16.8 Resource utilization questionnaire

Resource Utilization Questionnaire

Date of completion: ☐☐ ☐☐☐ ☐☐☐☐
DD MMM YYYY

During the past 4 weeks:

1. Has the subject been living in a Nursing Home? ☐ No ☐ Yes

If yes: how long has the subject been living in a Nursing Home during this period? ☐☐ Weeks

---

2. Has the subject been attending a Day Care Centre? ☐ No ☐ Yes

If yes:

1) How long has the subject been attending a Day Care Centre during this period? ☐☐ Weeks

2) On average, how many days per week has the subject been attending a Day Care Centre? ☐☐ Days

---

3. Has the subject received home health care services?

☐ No
☐ Yes

If yes:

1) In total, how long has the subject received home health care services during this period? ☐☐ Weeks

2) On average, how many hours per week has the subject received home health care services? ☐☐☐ Hours

---

4. Has the subject been hospitalized?

☐ No
☐ Yes

If yes: Please complete the reason for hospitalization(s) (or the main diagnosis received in connection with the hospitalization(s)) and the number of days the subject was in hospital in connection with (each of) the hospitalization(s) below:

Hospitalization Number	Reason/Diagnosis	Number of days in hospital
1		
2		
3		
4		

---

5. Has the subject visited or been visited by a physician?

☐ No
☐ Yes

If yes: how many times? ☐☐

16.9 Patient Reported Questionnaire Information Sheet

Subject Number ___ ___ ___ ___ ___/___ ___ ___ ___

Visit: _____

Instructions:

- This information sheet is to be completed by the study nurse/investigator.
- This information sheet must be competed for all patients at each visit in which the protocol requires the questionnaire to be administered, whether or not the questionnaire was completed by the patient.
- When the patient returns the questionnaire
  - Please complete this information sheet.
  - Please check that the patient has answered all the questions and no question has more than one answer.

1. Was the questionnaire provided to the patient at this visit? ☐ 1 No ☐ 2 Yes
   If YES, please continue
   If NO, please go to question 5

2. Date questionnaire completed

d	d	m	m	y	y	y	y

3. Was the questionnaire provided prior to clinical examination? ☐ 1 No ☐ 2 Yes

4. Were all questions answered? ☐ 1 No ☐ 2 Yes
   If YES, please STOP
   If NO, please continue

5. If No, specify reason questionnaire/questions was not answered:
   - ☐ Patient felt too ill
   - ☐ Patient refused to complete questionnaire for reason other than illness
   - ☐ Patient did not keep appointment
   - ☐ Questionnaire not administered due to institution error
   - ☐ Questionnaire not available in the appropriate language
   - ☐ Other, please specify: _____