COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: SMILOW CANCER HOSPITAL

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Study 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

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Invitation to Participate and Description of Project

You are invited to take part in a research study. The research study is designed to look at an investigational drug, radium-223 dichloride, to potentially treat metastatic breast cancer. You have been invited to take part because you have been diagnosed with a specific type of breast cancer, called HER2 negative hormone receptor positive breast cancer, and your breast cancer has spread to the bones (bone metastases)

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: the purpose and nature of the research study, the procedures that will be performed, the risks of the study drug(s) and procedures, possible benefits, possible alternative treatments, your rights as a participant and other information about the research study. You should take whatever time you need to discuss the research study with your physician and family. The decision to participate or not is yours. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign and date where indicated on this form.

If you choose to participate, you will be told of any significant new findings that develop during the course of your participation in this study that may affect your willingness to continue to participate.

The research study is being sponsored by Bayer HealthCare Pharmaceuticals Inc. Bayer HealthCare Pharmaceuticals Inc. is called the Sponsor and Yale University is being paid by Bayer HealthCare Pharmaceuticals Inc. to conduct this research study. Dr. Kerin Adelson is the principal investigator of this study at Yale Cancer Center.

Purpose

The purpose of this study is to understand if adding radium-223 dichloride to exemestane and everolimus helps subjects to delay the occurrence of symptomatic skeletal events (SSEs). The SSEs are defined as new symptomatic (i.e. painful) bone fractures due to bone metastases, spinal cord compression (pressure on the spinal cord causing symptoms such as pain, leg weakness, numbness, tingling, burning or other sensations), or requires surgery or radiation therapy delivered by an external machine to relieve bone related symptoms/signs. As your doctor explained to you, your breast cancer has spread to the bones (bone metastases). As one of the standards of care, subjects with breast cancer and bone metastases may receive treatment with exemestane and everolimus in addition to best supportive care (care given to a patient to help lessen symptoms caused by the disease). Currently, your doctor considers that standard of care therapy with exemestane and everolimus is an appropriate treatment for you.

The study drug that will be used in this research study, radium-223 dichloride, is investigational. This means it has not been approved for use by the United States Food and Drug Administration (FDA) in your type of cancer. Radium-223 dichloride has been approved in some countries for treatment of patients with prostate cancer and bone metastases, but is not approved for patients with breast cancer.

Radium-223 dichloride is a radioactive drug, that is administered through a vein and that is taken up by the bones after it is injected into the body. It gives off radioactivity, which is thought to kill the tumor cells that have spread to the bone. Radium-223 dichloride releases a type of radioactivity that travels a very short distance. As a result, most of the effects of the drug are limited to the bones, which is the location where your breast cancer has spread.

The amount of radioactivity in a dose of radium-223 dichloride is measured in kilo Becquerel (kBq). Each subject gets a radium-223 dichloride dose that is based on their weight measured in kilograms (kg). The dose of radium-223 dichloride that is approved by the FDA is 55 kBq per kilogram of weight. Each dose of radium-223 dichloride is administered through the vein, once every 28 days (a “cycle”), for six doses.

Normal saline is used as the placebo in this study. Normal saline is commonly used to provide fluids or to give medications. The volume of normal saline will be based on body weight measured in kilograms. Each dose of normal saline is administered by injection through the vein, once every cycle (28 days), for a total of six doses.

It is expected that approximately 311 female subjects will participate in this study at about 160

sites in around 21 countries. It is expected that approximately 10 female subjects will be enrolled at Yale Cancer Center.

Study Procedures

Tests and procedures that would be performed for your regular cancer care whether you are on this study or not, are called "standard of care." All of the tests and procedures listed below that will be performed at your study visits, should you choose to participate in this study, are standard of care unless noted with an asterisk (*).

This study is made up of four study periods: Screening/ Randomization, Treatment, Active Follow-Up with Clinic Visits and Active Follow-up without Clinic Visits.

Before deciding to participate, you should understand that this study is designed as a "randomized", "placebo-controlled", and "double-blind" study.

-"Randomized" means that you are put into a group by chance. It is like flipping a coin. Neither you nor the researchers will choose the group to which you are randomized. You will have an equal chance of being placed in any group.
-"Placebo controlled" means that this study uses a non-active drug (normal saline) which is called a placebo.
-"Double-blind" means that your study doctor, you, and most of the study staff will not know which drug you will receive. The Pharmacist will know it, but will not give this information to anyone who is involved in your care. This allows evaluation of the safety and effectiveness of the investigational study drug in a fair way. Neither you nor the investigator will know what group you are in but the study doctor can find out if medically necessary.

There will be two groups in this study. All study subjects will receive exemestane and everolimus as well as best supportive care according to your doctor prescription. The combination of exemestane and everolimus has been proven to be effective in patients with metastatic breast cancer which is growing despite prior standard treatments. In addition to the exemestane and everolimus, you will receive study drug or placebo, depending on which study group you are in:

1. Radium-223 dichloride administered by injection through the vein once every 4 weeks for a maximum of 6 cycles

2. Normal saline administered by injection through the vein once every 4 weeks for a maximum of 6 cycles

If you choose to participate and if you qualify for being randomized into the study, you will be assigned to one of the two study groups described above and below. Whether you receive radium-223 dichloride or normal saline (placebo) will be determined by a computer program.

Study Group 1: Radium-223 dichloride at a dose of 55 kBq per kilogram of body weight once every 28 days for a maximum of six injections through the vein, plus exemestane and everolimus therapy as prescribed by your doctor.

Study Group 2: A normal saline dose (placebo) once every 28 days for a maximum of six injections through the vein, plus exemestane and everolimus therapy as prescribed by your doctor.

For both study groups, participation in this study will involve multiple study visits and multiple telephone contacts (study periods and visit schedule described below in this form).

After you finish receiving radium-223 dichloride/placebo, you will continue to be treated with exemestane and everolimus or other therapies, following the recommendation of your study doctor.

You do not have to stay overnight for any visits at which you receive radium-223 dichloride/placebo. All injections can be given in the outpatient clinic.

The estimated total duration that you will receive radium-223 dichloride/placebo will be up to six months. During the first three cycles of receiving radium-223 dichloride/placebo (1 cycle = 28 days), you will need to come to the clinic on Day 1 and Day 15. During the last three cycles, you will have to come to the clinic on Day 1. You will receive radium-223 dichloride/placebo by injection into the vein and provided exemestane and everolimus (to take by mouth) on Day 1 of each cycle. In addition to your intravenous dose of radium-223 dichloride/placebo, you will have tests and blood collections; these are listed below in the sections for Screening/Randomization, Treatment Period and Active Follow-up.

Treatment with exemestane and everolimus will continue after completion of radium-223 dichloride/placebo until you experience disease progression, unacceptable toxicity or can no longer travel to the study site.

After 4 weeks from the last dose of radium-223 dichloride/placebo, you will have to come to the clinic. This visit includes a blood draw, scans of your chest, abdomen, pelvis, and bones, electrocardiogram (test to evaluate the electrical rhythm of your heart) review your pain medication diary and questionnaires.

If you did not experience a SSE during the radium-223 dichloride/placebo treatment period, the following visits will continue with the same frequency as before (every 4 weeks) until you have a SSE. After the occurrence of the SSE, you will be switched to a frequency of visits every 8 weeks. Blood draws, scans of your chest, abdomen, and bones and electrocardiograms* (test to evaluate the electrical rhythm of your heart) will be performed every 8 weeks and the scans of your bones every 12 weeks. Once you are discontinued from all study treatments, an End of Treatment visit will be conducted within 4 weeks.

After the end of treatment visit, follow-up evaluations by clinic visits or phone calls will be conducted on a regular schedule. Depending on whether you have already experienced an

SSE/bone progression or not, the schedule of these clinic visits/phone calls may vary as follows:

- every 4 weeks – before you experienced an SSE
- every 8 weeks – after you experienced an SSE

If you can no longer travel to the clinic, you will be contacted by the study staff by phone at one of the above mentioned intervals. They will ask how you are, if you have had adverse events, if you have started chemotherapy, if you have had any SSEs (if not already had one), and other questions about your health. If you start chemotherapy, the study staff will call during chemotherapy treatment and for the first six months after treatment to ask about specific adverse events.

The clinic visits/telephone follow-up calls will continue every 4 or 8 weeks until you withdraw informed consent or the study end is decided.

Screening Period

If you agree to participate and sign and date this form, you will need to undergo a series of tests and procedures to determine if you are eligible to participate in the research study. You will come to the study site for screening tests up to 21 days before you are randomly assigned to Study Group 1 or Group 2 and it is possible that more than one screening visit may be needed.

The study doctor will ask you questions about your age, your ethnicity, and about your medical history, both general and related to your breast cancer. The study doctor will also collect information about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies, and your prior and current breast cancer treatments. Some tests (e.g., CT scan, MRI scan, bone scan) will not be repeated if done within the prior 3 weeks from the date of randomization.

The following tests or procedures will be performed during the visit(s):

- You will have some blood taken (approximately 25mL or 5 teaspoons) for laboratory tests*. If you are able to become pregnant, you will have a blood pregnancy test* 7 days prior to randomization before first to check that you are not pregnant before entering the study. For women who have had ovarian ablation or medical ovarian suppression, as well as post-menopausal women younger than 55 years of age and one year or more of amenorrhea and no ovarian suppression must also have an estradiol assay* (test to check the level of ovarian hormones in the blood) within 7 days prior to randomization.
- You will have a physical exam, and your height, weight, and vital signs will be measured (blood pressure, respiratory rate, and heart rate and body temperature).
- You will have an electrocardiogram*. This is a test to evaluate the electrical rhythm of your heart (if one has not been performed within 3 weeks of randomization).
- You will be asked about any new complication or symptom related to your bones or treatment for those complications, including the use of radiation therapy or surgery to fix damaged bones, the occurrence of bone fractures resulting from your breast cancer bone metastases, and spinal cord compression.
- You will have a CT scan or MRI scan to assess the status of your breast cancer in the chest,

abdomen and pelvis. Your doctor will inform you of the location where the study imaging will take place (if one has not been performed within 3 weeks of randomization).
- You will have a Technetium-99m bone scan or ^{18}F-sodium fluoride PET/CT scan or FDG PET/CT scan to assess the location(s) and status of your breast cancer in the bone. For this scan, you will get an injection of a tracer material (technetium, sodium fluoride, or sugar based) to get images of your bones with greater detail. These images will help your study doctor to assess the status of your tumors before you receive radium-223 dichloride/placebo. Your doctor will inform you of the type of bone scan and the location where all study imaging will take place (if one has not been performed within 3 weeks of randomization).
- Any changes in your health that developed from the time you signed the Informed Consent Form will be assessed.
- Instructions to be followed by you and your family after each injection of radium-223 dichloride/placebo will be reviewed (see Radiation Safety on page 13).
- After the screening tests are completed, your study doctor will review them.
- If you are considered eligible, you will be randomized into the study. Your study doctor will inform you when you should come to the clinic to have your blood samples collected (approximately 25mL or 5 teaspoons) and when you should come to the clinic to begin receiving radium-223 dichloride/placebo in this study.

Treatment Period
Your study doctor will discuss with you what will happen during study visits.

Before you come to the clinic for your first time receiving radium-223 dichloride/placebo, you will have been randomly assigned to Study Group 1 or Group 2. Your study doctor, you, and most of the study staff will not know which combination of study drug or placebo and standard of care hormonal therapy you will receive. The Pharmacist will know, but will not give this information to anyone who is involved in your care.

If your study doctor has determined that you are eligible for this study, and you were randomized into the study, **the following procedures will take place on Day 1 of every cycle (except as marked).** A cycle is a time period of 28 days.

- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.
- You will have a physical exam, and your weight and vital signs will be measured (blood pressure, respiratory rate, and heart rate and body temperature).
- The day before the administration of radium-223 dichloride/placebo, you will start completing a diary* with questions related to the pain relief medications you take. Additionally, on the day of radium-223/placebo administration and prior to any study procedures or seeing your study doctor, you will have to complete a questionnaire* related to the pain you experience.
- You will be asked about any new complications related to your bones or study drug combination for complications, and the occurrence of bone fractures resulting from your breast cancer, or spinal cord compression.

- The doctor will confirm you are still eligible to continue your assigned medications; exemestane and/or everolimus dose levels may be changed if your doctor thinks this is in your best interest.
- Radium-223 dichloride/placebo will be administered to you via injection* (based on your studygroup assignment).You will receive your supply of exemestane and everolimus therapy to take every day for the next 28 days (until you experience disease progression, unacceptable toxicity or can no longer travel to the study site). You will be asked to bring any remaining medications back to the clinic at your next visit, and you will be asked questions about taking these medications.
- The study doctor will inform you when you should come back to the clinic for the procedures for Day 15 or Day 1 of the next cycle.
- Your study doctor will review the instructions to be followed by you and your family after each injection of radium-223 dichloride/placebo. The patient information card will be provided to you to carry until the next visit.
- You will have some blood taken* within 5 days prior to the dose (approximately 25mL or 5 teaspoons) for safety laboratory tests as well as a pregnancy test if you are able to become pregnant. On C1 and C4 you will have some blood (approximately 35mL or 7 teaspoons) taken* within 5 days prior to the dose to measure markers related to your disease in your blood, to see if the markers change during treatment, and to compare the level of markers with how well your assigned treatment may work and how safe it is. Additional blood samples (10 ml) will be collected on C2, C3, C5 and C6 for the same purpose.
- On C1 and C4 you will also provide a urine sample* to measure markers related to your disease in your urine, to see if the markers change during the time you receive radium-223 dichloride/placebo drug, and to compare the level of markers with how well your assigned combination of study drug and hormonal therapy may work and how safe it is in your urine.
- Every 8 weeks (+/- 7 days) after first Ra223/placebo administration, until radiological progression of your breast cancer is documented, you will undergo CT or MRI scan of the chest, abdomen and pelvis. A Technetium-99m bone scan or ^{18}F-sodium fluoride PET/CT scan or FDG PET/CT scan will be done 8 weeks after the first dose and then every 12 weeks. These images will help your study doctor to assess the status of your tumor.
- You will have an electrocardiogram* test done (Day 1 of Cycle 3 and Cycle 5).

The following procedures will take place on Day 15 of the first three cycles:

- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.
- Your vital signs will be measured (blood pressure, respiratory rate, and heart rate and body temperature), and weight measured.
- You will be asked to bring exemestane and everolimus medications back to the clinic, and you will be asked questions about taking these medications.

- The study doctor will inform you when you should come back to the clinic for the procedures for Day 1 of the next cycle. You will be reminded to start completing a diary* the day before your visit with questions related to the pain relief medications you take.

You will have some blood taken (approximately 5 mL or 1 teaspoon) for safety laboratory tests (Cycles 1 and 2).

Four weeks after last dose of radium-223 dichloride/placebo injection, you will be requested to attend the clinic in order to perform the same common procedures done at Day 1 of each cycle. Additionally:

- An electrocardiogram test* will be done
- Some blood (approximately 25mL or 5 teaspoons) will be taken* within 5 days prior to the visit to measure markers related to your disease in your blood, to see if the markers change during the time you receive radium-223 dichloride/placebo, and to compare the level of markers with how well your assigned study combination may work and how safe it is.
- You will also provide a urine sample* to measure markers related to your disease in your urine, to see if the markers change during the time you receive radium-223 dichloride/placebo, and to compare the level of markers with how well your assigned study combination may work and how safe it is in your urine

Treatment with exemestane and everolimus will continue after completion of radium-223 dichloride/placebo until you experience disease progression, unacceptable toxicity or until you can no longer travel to the site.

End of Treatment

An End of Treatment Visit will be performed 4 weeks post-discontinuation or completion of all study treatments. After the End of Treatment Visit, you can continue with the Active Follow-up phase (described below):

- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.
- You will have to complete a questionnaire* related to the pain you experience.* The day before your visit and on the morning that you visit the clinic, you will start completing a diary* with questions related to the pain relief medications you take.
- You will undergo CT or MRI scan of the chest, abdomen and pelvis, and a Technetium-99m bone scan or 18F-sodium fluoride PET/CT scan or FDG PET/CT scan if no scan was done in the previous 8 weeks. These images will help your study doctor to assess the status of your tumor.
- You will have a physical exam, and your weight and vital signs will be measured (blood pressure, respiratory rate, and heart rate and body temperature).

- You will have some blood taken (approximately 25mL or 5 teaspoons) for safety laboratory tests.
- You will have some blood (approximately 35mL or 7 teaspoons) taken* within 5 days prior to the visit to measure markers related to your disease in your blood, to see if the markers have change during the time you receive radium-223 dichloride/placebo, and to compare the level of markers with how well your assigned study combination has worked and how safe it was. If you were able to become pregnant during the study, you will have a blood pregnancy test*.
- You will provide a urine sample* to measure markers related to your disease in your urine, to see if the markers change during the time you receive radium-223 dichloride/placebo , and to compare the level of markers with how well your assigned study combination may work and how safe it is in your urine.
- You will have an electrocardiogram test* done.
- You will be asked about any new complications related to your bones or treatment for complications, and the occurrence of bone fractures resulting from your breast, or spinal cord compression.

Follow-up Period

Active Follow-Up with Clinic Visits

If during the treatment period you did not experience a SSE and radiological progression of the tumor and if after the End of Treatment visit you are able to travel to the site, you can participate in the Active Follow-up with Clinic Visits. Visits will take place every 4 weeks (until you experience an SSE) or every 8 weeks (after you experienced an SSE). During each visit the following information will be collected:

- You will be asked to complete questionnaires (answer questions) about your use of pain relief medications* and how much pain you experience*.
- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.
- You will have a physical exam and vital signs will be measured (blood pressure, respiratory rate, and heart rate and body temperature) every 8 weeks.
- You will have some blood taken (approximately 25mL or 5 teaspoons) for safety laboratory tests every 8 weeks.
- You will undergo every 8 weeks a CT or MRI scan of the chest, abdomen and pelvis, and a Technetium-99m bone scan or ^{18}F-sodium fluoride PET/CT scan or FDG PET/CT scan every 12 weeks until radiological disease progression is documented. These images will help your study doctor to assess the status of your tumor.

Active Follow-Up without Clinic Visits

If you experienced an SSE and radiological progression of the tumor after the End of Treatment visit or after any active follow-up with clinic visit you are no longer able to travel to the site or if you missed 2 consecutive visits at which you were supposed to receive the study drug

combination, you can participate in the Active Follow-up without Clinic Visits. The study nurse, study doctor, or someone else from the clinic will contact you every 4 weeks (until you experience an SSE) or every 8 weeks (after you experienced an SSE). During each contact the following information will be collected:

- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.

End of Active Follow up

This visit will be performed only once, either at the end of the active follow-up with clinic visits or at the end of the active follow-up without clinic visits.
End of the active follow-up with clinic visits- the following procedures will be conducted:

- You will be asked to complete questionnaires (answer questions) about your use of pain relief medications* and how much pain you experience*.
- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.
- You will have a physical exam and vital signs will be measured (blood pressure, respiratory rate, and heart rate and body temperature).
- You will have some blood taken (approximately 25mL or 5 teaspoons) for safety laboratory tests.
- If you have not yet had a radiologically documented progression of your breast cancer you will undergo a CT or MRI scan of the chest, abdomen and pelvis, and a Technetium-99m bone scan or ^{18}F-sodium fluoride PET/CT scan or FDG PET/CT scan. These images will help your study doctor to assess the status of your tumor.

End of the active follow-up without clinic visits - the following procedures will be conducted:

- You will be asked questions about any new symptoms or illnesses, and any changes in your health and medications, since your last study visit.
- Your study doctor will ask if you have received any therapy for your breast cancer other than study drug since the previous visit, as well as the use of pain medication if you have bone pain.

Dose delay– study drugs:
If your study doctor tells you that any of your study drugs need to be delayed due to adverse events, you will be asked to come into the clinic for regular safety assessment to ensure recovery is progressing. Your dose level for radium-223 dichloride/placebo will not change during the study; however administration can be delayed if necessary. If your radium-223 dichloride/placebo intravenous dose is delayed by more than 4 weeks (cannot be more than 8 weeks between injections), you will not be allowed to continue to receive radium-223

dichloride/placebo.

Responsibilities as a Study Participant

If you decide to participate in this study, it is important that you agree to:

- Follow all instructions provided by your study doctor or the study staff associated with your study combination
- The day before your visit you will start completing a diary with questions related to the pain relief medications you take. Keep your study appointments. As soon as you know that you will be unable to keep an appointment, please contact your study doctor or the study staff to make a new appointment.
- Truthfully answer to your study doctor or the study staff when asked about any adverse events, visits to other doctors or hospital admissions, changes in your medications, including freely available medication.
- Inform the study doctor about any other studies or research you are currently taking part in
- Do not take part in any other research study without the consent of your study doctor while participating in this study, to avoid any possible interaction between the study drugs/devices.
- Tell the study doctor if you believe you may be pregnant.
- Tell your study doctor or research study staff if you change your mind about participating in the study.
- Your study doctor will give you a copy of the Instructions for Patients for this study. Please review and follow the instructions during the course of the study after each radium-223 dichloride/placebo injection. If you have any question, please discuss them with your study doctor.

Potential Risks, Side Effects, Discomforts and Inconveniences

While in this study, you may have side effects associated with radium-223 or placebo administration or due to exemestane and everolimus. Anticipated side effects of radium-223 and placebo are listed here. Please speak with your doctor about the risks of the standard of care drugs, exemestane and everolimus. In addition to the risks listed below, there may be risks that are currently unknown. If significant new risks develop during the course of study that might affect your willingness to participate, information will be reported to you as soon as possible. Possible side effects that you may experience during this study will be fully explained to you by the study staff. Please ask as many questions as you want so that you can understand the possible side effects of your specific study combination before you decide whether you want to be in this study. Please ask the study doctor or the study staff to explain any information or words that are not clear to you. We ask you to consider carefully the possible risks or discomforts before you agree to participate in this study.

Side effects associated with the study drug, radium-223 dichloride:

The following side effects of the study drug have been observed in previous testing:

- The side effects that occurred very commonly (in ≥10 out of 100 subjects) are: nausea, vomiting, diarrhea (usually mild) and thrombocytopenia (lowering of blood platelet counts which may increase the risk of bleeding).
- The side effects that occurred commonly (in ≥1 but <10 out of 100 subjects) are:
- Leukopenia and neutropenia (lowering of white blood cell counts which may increase the risk of infection)
- Pancytopenia (lowering of all blood cell lines)
- Injection site reactions (e.g., redness of the skin, pain and swelling).
- The side effect that occurred uncommonly (in ≥1 out of 1000 subjects but <1 out of 100 subjects) is lymphopenia (decrease in the number of specific type of white blood cells).

It is important to be aware that there may be other side effects that are not yet known and cannot be foreseen. Side effects may go away after you stop receiving the study drug combination, but it is also possible that side effects may last a long time or forever. They may range from mild to life threatening. Therefore, it is important to tell the study doctor or study nurse immediately about any changes in health that may have occurred even if you do not think they are related to the study. All intravenous injections have a slight risk of pain, bruising, bleeding, infection, and rarely, fainting and/or nerve damage. Your study doctor may give you treatment to help control side effects.

As the study drug, radium-223 dichloride, is under development, there may be side effects, including allergies, which are not yet known. Therefore you must notify your study doctor of any new symptoms that you may have.
Increased risk of developing cancerous bone tumors has been reported following exposure to different forms of radiation (including radioisotopes). However, no such cases have been reported in clinical studies with radium-223 dichloride.

In addition, the effect of radium-223 dichloride on the subject's fertility is unknown.

Exemestane:

A brief summary of expected side effects is summarized below:

Very common side effects, (affecting more than 1 person in 10):

- Difficulty sleeping
- Headache
- Hot flushes
- Feeling sick
- Increased sweating
- Muscle and joint pain (including osteoarthritis, back pain, arthritis and joint stiffness)
- Tiredness

Common side effects, (affecting between 1 to 10 people in 100):

- Loss of appetite
- Depression

- Dizziness, carpal tunnel syndrome (a combinations of pins and needles, numbness and
- Pain affecting all of the hand except the little finger)
- Stomach ache, vomiting (being sick), constipation, indigestion, diarrhoea
- Skin rash, hair loss
- Coughing
- Thinning of bones which might decrease their strength (osteoporosis). This may raise your risk of bone fractures (breaks or cracks) Pain, swollen hands and feet

Uncommon side effects, (affecting between 1 to 10 people in 1000):

- Drowsiness
- Generalized weakness

Everolimus

A brief summary of expected serious side effects is summarized below:

Very common (may affect more than 1 in 10 people)

- Increased temperature, chills (signs of infection)

- Fever, coughing, difficulty breathing, wheezing (signs of inflammation of the lung, also known as pneumonitis)

Common (may affect up to 1 in 10 people)

- Excessive thirst, high urine output, increase appetite with weight loss, tiredness (signs of diabetes)
- Bleeding (haemorrhage), for example in the gut wall
- Severely decreased urine output (sign of kidney failure)

Uncommon (may affect up to 1 in 100 people)

- Fever, skin rash, joint pain and inflammation, as well as tiredness, loss of appetite, nausea, jaundice (yellowing of the skin), pain in the upper right abdomen, pale stools, dark urine (may be signs of hepatitis B reactivation)
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of heart failure)
- Swelling and/or pain in one of the legs, usually in the calf, redness or warm skin in the affected area (signs of blockade of a blood vessel (vein) in the legs caused by blood clotting)
- Sudden onset of shortness of breath, chest pain or coughing up blood (potential signs of pulmonary embolism, a condition that occurs when one or more arteries in your lungs become blocked)
- Severely decreased urine output, swelling in the legs, feeling confused, pain in the back (signs of sudden kidney failure)
- Rash, itching, hives, difficulty breathing or swallowing, dizziness (signs of serious allergic reaction, also known as hypersensitivity)

Rare (may affect up to 1 in 1000 people)

Shortness of breath or rapid breath (signs of acute respiratory distress syndrome)

Other Risks and Side Effects

Normal saline (placebo) injections through the vein:

There are no known side effects of normal saline that you will receive. All injections into your vein have a slight risk of pain, bruising, bleeding, infection, and rarely, fainting and/or nerve damage.

Radiation Safety:
You will not know, and your study doctor will not know, if you have been randomly assigned to the group that will receive radium-223 dichloride. You need to understand the risks of radiation in case you receive radium-223 dichloride. There is no risk of radiation if you are randomized to

receive the normal saline however you will not know which study drug combination you will receive.

In general, the administration of radioactive drugs involves a potential risk for third parties (people other than the subject), due to radiation coming from the subject's body and due to possible contamination due to spilling of the subject's bodily fluids, such as urine or faeces. When radium-223 dichloride is given by an intravenous injection to a subject, the risk for external radiation exposure to others is very low. The type of radiation from radium-223 dichloride only travels a small distance within the body, so it does not exit your body. In addition, any radium-223 dichloride in your stool or urine does not present a significant risk to others if standard hygiene measures are followed. Your doctor will provide additional information about precautions to take after you have received radium-223 dichloride/placebo.

As with any radiotherapy treatment, there is also a risk of late side effects occurring months or years after the treatment period. It is important to let your study doctor know of any changes to your health while you are receiving the study combination or during follow up on this research study.

Blood Collection and Intravenous (IV) catheter placement:
The risks of taking blood may include pain, redness, swelling and/or bruising where the needle enters your body, light-headedness and fainting. On rare occasions, local blood clot formation or infection with redness and irritation of the vein has occurred. The blood pressure cuff may cause discomfort or bruising to the upper arm. Approximately 285 mL of blood will be taken for research purposes only for a subject who completes all six cycles and the End of Treatment visit. Over the Active Follow-up with Clinic Visits period, additional 25 mL of blood will be collected each visit.

Electrocardiogram (ECG):
An ECG is an electrical tracing of your heart's activity. During the procedure, you will have electrodes (small sticky patches) placed on your chest skin and wires attached to them. There may be some pulling on your skin or irritation, similar to pulling off an adhesive bandage, when the patches are removed.

Reproductive Risks:

There are unforeseeable risks associated with your participation in the study if you become pregnant or try to. The Study Sponsor recommends that you and your partner use a reliable and acceptable birth control method during the study and for six months after end of treatment period. Please discuss these appropriate contraceptive measures with the study doctor.

If you become pregnant during the study, please inform your study doctor immediately.

Female participants

The effects of the study drug on an unborn child and on a breast-fed baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the study. You will not be eligible to participate in the study if you are pregnant, trying to become pregnant, or breast-feeding. To avoid any risks, the study doctor will take the following precautions:

The study doctor will ask you to undergo a serum (blood) pregnancy test* prior to the start of the study. If you are a woman who has had ovarian ablation or medical ovarian suppression or if you are a post-menopausal woman younger than 55 years of age and one year or more of amenorrhea and no ovarian suppression, you will have an estradiol assay* (test to check the level of ovarian hormones in the blood).

If you are of child-bearing potential and if you are sexually active, you and/or your male partner will be required to use a reliable and acceptable birth control method during the course of the study and for a period of 6 months after the completion of the final clinic visit of the study. Two methods of contraception must be used simultaneously. The possible options are:

a) Condoms (male or female) in combination with a spermicidal agent;

b) Diaphragm or cervical cap with spermicide in combination with a highly effective non-hormonal birth control method such as IUD (intra-uterine device).

The study doctor will advise you on the use the most appropriate birth control method for you.

If you do become pregnant while participating in the study you should advise your study doctor immediately. Your study doctor will withdraw you from the study and advise on further medical attention should this be necessary. Information on your pregnancy and the birth of the child may be collected by the sponsor for the purpose of evaluating the study drug's effects on the pregnancy and child.

There may also be side effects, other than listed above that we cannot predict. Treatment may be offered to make side effects that occur less severe and less uncomfortable. Many side effects go away shortly after the drug or procedure is stopped, but in some cases side effects can be serious, long lasting or permanent.

For more information about risks and side effects, ask the researcher or contact their office at (203) 200-1689.

Benefits

If you agree to take part in this research study, we cannot guarantee that you will receive any benefits. We hope the information learned from this research study may benefit other patients with metastatic breast cancer that has spread to the bones in the future. Your participation will help doctors to better understand the efficacy and safety of the study drugs.

Economic Considerations

You will not be paid for taking part in this study. Tests and procedures that would be performed for your regular cancer care whether you are on this study or not are called "standard of care."

All of the tests and procedures listed in this consent form that will be performed at your study visits are standard of care unless noted with an asterisk (*). There will be no charge to you or your insurance provider for the study drug, radium-223 dichloride, or the placebo. There will be no charge to you or your insurance provider for tests or procedures noted with an asterisk as these are performed for study purposes only. All other tests and procedures will be charged to you or your insurance provider in the usual way as these are standard of care. This may include other tests and procedures not listed in this consent if your doctor feels it is necessary for your care, such as additional laboratory tests.

Taking part in this research study may lead to added costs for you or your insurance provider. You are encouraged to speak with your insurance provider prior to entering the research study to find out your individual coverage. If you have difficulty determining your individual insurance coverage, you may call Dr. Kerin Adelson's office for assistance at (203) 200-1689.

You or your insurance provider will be charged for continuing medical care and/or hospitalization that are not a part of the research study.

Treatment Alternatives

You do not have to participate in this study. Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Receiving no treatment at this time.
- Getting comfort care, also called palliative care; this type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer.
  Comfort care does not treat the cancer directly but instead is meant to improve how you feel. Comfort care tries to keep you as comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Confidentiality and Authorization to collect, use and disclose Protected Health Information

For purposes of this study, Yale University, Yale-New Haven Hospital, and Dr. Kerin Adelson will use medical information collected or created as part of the study, such as medical records and test results, which identifies you by name or in another way. Your consent to participate in the study means you agree that Yale University, Yale-New Haven Hospital, and Dr. Kerin Adelson may obtain your medical information that they request for study purposes from your physicians and your other health care providers from the past or during your participation in the study.

The protected health information that will be collected in this study includes date of birth (day, month and year), your initials, your sex, your ethnic origin and information on your physical or mental health or condition (including any study photographs).

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases such as HIV or hepatitis. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the study staff will get information that identifies you and your protected health information. This may include information that might directly identify you, such as your name, date of birth, and medical record number**.** This information will be de-identified prior to providing it to the sponsor, meaning we will replace your identifying information with a code that does not directly identify you. The study doctor will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the Principal Investigator or selected members of the study team. Any information that can identify you will remain confidential.

The records for this trial will be stored in locked cabinets and/or offices and password protected computers. The study team will only give this coded information to others to carry out this research study or to sponsor representatives to comply with federal laws and regulations. It is anticipated that records containing the information that links you to your coded information will be maintained indefinitely, as there are no plans at this time to destroy these records at the end of the study.

During your participation in the study, data (including samples) will be collected. All data collected will be encoded (identified with a number) in order to ensure that your identity will be kept confidential. Only your doctor holds the information that allows the number to be linked to your name.

The encoded data will be analyzed and prepared for submission to Competent Authorities. The data will be transferred to the pharmaceutical company and/or to companies within the group of companies of the pharmaceutical company and/or to third parties who perform services for the pharmaceutical company. These companies will use the data in accordance with the purposes of the study as well as for submission to competent authorities.

Representatives of the pharmaceutical company, Competent Authorities or ethics committee staff may require access to your medical records with your personal data (un-coded) to ensure the study is properly conducted and that the data collected is correct. These individuals are obligated to ensure your confidentiality is maintained.

In the US, Cardinal Health will be dispensing the doses of radium-223 dichloride to the study sites; they will have your name and body weight in their records for this purpose.

During your participation in the study, radiological images (i.e., CT scan, MRI scan, bone scan)

will be taken from you.

These images will be encoded in the same way as your data.

Your images will be used to assess the status of your breast cancer and breast cancer in the bone and may also be sent to contract service providers of the sponsor who will evaluate them.

In general, such service providers will receive the images in encoded form. However, in some cases due to the equipment your identifying data cannot be deleted before sending the images to such service providers. In this case, such service provider will encode the images before evaluation.

The images taken during the examination of MRI or CT will contain personal data that can identify you, and these may be sent to third-party company, for evaluation and/or storage. The images containing your personal data will not be sent to anyone else and the third-party company will delete your personal data from the images before storing or evaluating.

The results of the study (including the information collected from you) will be processed, analyzed, and reported to Bayer HealthCare, or their representative, who are responsible for processing and keeping the data. The written study result may be submitted to Competent Authorities to help them decide if radium-223 dichloride as treatment for breast cancer can be approved to go on the market. The results will be published in scientific articles. All information in reports/publications will be coded and you will not be identified in person. If your personal data is disclosed to a third party, all appropriate measures will be taken to protect such data.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g., health insurance company, disability provider.)

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee or Institutional Review Board that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential
- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The study doctor, Dr. Kerin Adelson, and the Yale study team
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may

also be used to meet the reporting requirements of drug regulatory agencies.

- The study sponsor or manufacturer of study drug, Bayer HealthCare Pharmaceuticals Inc. and the people and companies that they use to monitor, administer, or conduct the research
- A Contract Research Organization and its employees who are monitoring, administering and conducting the research on behalf of Bayer HealthCare Pharmaceuticals Inc. A contract research organization is an independent entity with which a research sponsor contracts to oversee and facilitate various aspects of the clinical research process on the research sponsor's behalf.
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at Yale School of Medicine and Yale-New Haven Hospital is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Authorized representatives of the Food and Drug Administration (FDA**)** and the manufacturer of the study drug being tested, Bayer HealthCare Pharmaceuticals Inc., may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others.

The sponsor will see the research information we collect about you when they come to Yale to monitor the conduct of this research study. The "Sponsor" includes any persons that work for or are hired by the sponsor to conduct research activities related to this study. For this study the sponsor is Bayer HealthCare Pharmaceuticals Inc. Yale researchers will also send the sponsor your health information during the study or at the end of the study. When Yale researchers send information about you to the sponsor, they will not send information that directly identifies you such as your name.

You have the right to review and copy your health information in your medical record in

accordance with institutional medical records policies. However, you will not be allowed to look at or copy your study related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

results from this study might be transferred to countries outside the US, for application for international registration in these countries. In that case your identity will still remain confidential.
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

If you become ill or are physically injured due to the study drug, radium-223 dichloride, placebo, exemestane and everolimus or any investigational procedure specifically required by the plan for this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study drug(s) or properly performed non-standard of care investigational procedure required by the study will be covered by the Sponsor as long as you have followed the directions of the study doctor. The Sponsor is not responsible for expenses that are due to pre-existing medical conditions, underlying disease or procedures which would have been performed even if you were not participating in the Study.

If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the study doctor.

You will not receive any other kind of payment. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study. You do not give up any of your legal rights by signing this consent form.

New Information

During the study, new information about the risks and benefits of the project may become known. Your study doctor will discuss with you any important new information developed during the course of the study that may affect your willingness to continue to participate in the study. This new information may also mean that you can no longer participate in this research. In all cases, you will be offered all available care to suit your needs and/or medical condition.

Voluntary Participation and Withdrawal

Participation in this study is voluntary. You are free to choose not to take part in this research

study. Refusing to take part in this research study will not lead to penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study:
If you decide to participate in this research study, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. They will make sure that proper procedures are followed and a final visit is made for your safety.

You have the ability to discontinue only the study treatment period but still participate in the study follow-up. We would request you to undergo study examinations after your discontinuation of treatment period, as noted in the section on End of Treatment visit. You will continue to be contacted, as described above for Active Follow-up with or without clinic visits, unless you have expressly informed your study doctor in writing that you no longer agree to the follow up measures.

In the event that you decide to withdraw from the study treatment period, we would request that you undergo study examinations as described in the section on Active Follow-Up, done by your study doctor after your withdrawal.

The data that have been collected until the time of your withdrawal will be kept. In addition, it is of high importance to collect further follow-up data on your health, evaluate the radiological images and/or blood samples already taken from you as described in the Study Protocol. The reason is to enable a complete and comprehensive evaluation of the study and study drug and to comply with legal and regulatory recording and reporting requirements.

Therefore you are asked to give your consent to such data collection/analyses follow-up measures. In case you do not want us to collect further information after your withdrawal, you should explicitly inform your study doctor about that and sign a separate consent to terminate the follow-up.

The researchers may withdraw you from participating in the research if necessary. This study may be stopped or you may be withdrawn from receiving radium-223 dichloride/placebo without your consent for a variety of reasons.

The *sponsor* can stop the study or put the study on hold because of the following reasons:

- The risks of continued treatment are much greater than any possible benefits, based on information from this study or other studies
- The study ends
- Decisions made in the commercial interests of the sponsor.
- Decisions made by the Regulatory Authorities or Ethics Committees.

The *study doctor* can withdraw you from receiving radium-223 dichloride/placebo because of the following reasons:

- If continued participation in the study is not beneficial to you in your doctor's opinion
- If you develop unacceptable side effects
  - If you develop an illness that makes receiving radium-223 dichloride/placebo too risky
  - If your breast cancer progresses and your doctor believes that radium-223 dichloride/placebo is no longer working
- If you are unable or unwilling to meet the requirements of the study such as keeping appointments and taking medications as directed.
- If you need to take other treatments that are not allowed
- If your next dose is delayed by more than 4 weeks (maximum of 8 weeks between injections of radium-223 dichloride/placebo) for any reason.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.

If you fail to give your consent by not signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

Withdrawing Your Authorization to Use and Disclose Your Health Information:
You may withdraw or take away your permission to use and disclose your health information at any time. You do this by telling the study staff or by sending written notice to the study doctor, Dr. Kerin Adelson, at the address listed on page one of this form. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project as described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to participate in this research.

I also confirm that I have received a Trial Alert Card providing contact details of the study doctor and agree to carry this card with me at all times.

Study Participant (print name)	Signature	Date
Person obtaining consent (print name)	Signature	Date
Person obtaining consent (print name) – only if applicable, otherwise blank	Signature	Date
Interpreter/ Witness (print name) – only if applicable, otherwise blank	Signature	Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Kerin Adelson, at (203) 200-1689. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.