SUMMARY OF CHANGES – Consent

NCI Protocol #: 10302
CCC Protocol #: PhII-200
Protocol Version Date: September 11, 2024

Protocol Title: Phase II Trial of Radium-223 Dichloride in Combination with Paclitaxel in Patients with Bone Metastatic Breast Cancer.

Informed Consent Version Date: September 11, 2024

1.	Page 1	Updated ICF date from 8/7/2023 to 9/11/2024 **There are no additional changes made to this document.**

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of Radium therapy (Radium-223 Dichloride) to a usual chemotherapy treatment (paclitaxel) for advanced breast cancer spread to the bones

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10302, "Phase 2 trial of Radium-223 Dichloride in combination with paclitaxel in patients with bone metastatic breast cancer" (NCT # NCT04090398)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have advanced breast cancer that has spread to your bone.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can we lower the chance of your breast cancer growing by adding therapy with Radium-223 dichloride to the usual chemotherapy with paclitaxel?
We are doing this study because we want to find out if this approach is better or worse than the usual approach for your breast cancer. The usual approach is defined as care most people get for metastatic breast cancer that has spread to the bone.

What is the usual approach to my metastatic breast cancer?

The usual approach for patients who are not in a study is treatment with chemotherapy or hormonal therapy that has been approved by the Food and Drug Administration (FDA). One such chemotherapy is paclitaxel, which is included in this study. Sometimes, combinations of these drugs are used. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above. You may choose the available options of hormone therapy, CDK4/6 inhibitors, or standard chemotherapy treatment that may be beneficial for your cancer treatment.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will be randomly (like the toss of a coin) selected to either get the combination of Radium-223 dichloride and paclitaxel or get paclitaxel alone (usual care). For participants receiving the combination treatment, after you complete all the Radium-223 dichloride infusions (about 6 months), you will remain on therapy with paclitaxel until your disease worsens, the side effects become too severe, or you choose to no longer participate in the study. For participants receiving paclitaxel alone, you will continue to receive therapy until your disease worsens, the side effects become too severe, or you choose to no longer participate in the study.

After you finish your treatment with Radium-223 dichloride and paclitaxel or paclitaxel alone, you will be asked to complete a safety follow-up visit approximately 30 days after your last dose of treatment. Your doctor or the study team will continue to be in contact with you via a phone call or review of your medical record every 3 months for 2 years to follow your condition.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the Radium-223 dichloride and paclitaxel combination may not be as good as the usual approach for your cancer at shrinking or controlling your cancer.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Low number of red blood cells (anemia) that may require a blood transfusion
- Low number of white blood cells (leukopenia, lymphopenia, neutropenia) which help your immune system and may increase the risk of infection
- Low number of platelets (thrombocytopenia) which may cause bleeding or bruising and may require a transfusion
- Diarrhea or nausea
- Tiredness

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that this combination of Radium-223 dichloride and paclitaxel may be effective in shrinking or controlling your type of cancer. It is not possible to know now if the study treatment will extend your life compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.

- The study is stopped by the Institutional Review Board (IRB), FDA, or study sponsor (National Cancer Institute [NCI]). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment (chemotherapy with paclitaxel) alone to using Radium-223 dichloride plus the usual treatment (chemotherapy). The addition of Radium-223 dichloride to the usual treatment could shrink or control your cancer. But, it could also cause side effects, which are described in the risks section below.

Radium-223 dichloride is a radioactive drug that behaves in a similar way to calcium and collects in cancer that has spread to the bones (bone metastases). The radioactive particles in Radium-223 dichloride act on bone metastases, killing the tumor cells and reducing the pain that they can cause. If there are cancer cells in more than one area of bone, the radium can work well to treat all those areas at the same time.

Radium-223 dichloride is an investigational radioactive drug that behaves in a similar way to calcium and collects in cancer that has spread to the bones (bone metastases). "Investigational" means that the study drug has not been approved by the FDA for your type of cancer.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the addition of Radium-223 dichloride increases the time before tumor starts growing or new lesions develop by 3.5 months or more compared to the usual approach.

Radium-233 dichloride is already approved by the FDA for use in advanced prostate cancer. There will be about 70 people taking part in this study.

What are the study groups?

This study has 2 study groups. You will be told which group you are in.

- **Group 1**

  If you are in this group, you will get the combination treatment with Radium-223 dichloride and paclitaxel. Radium-223 dichloride is given through a vein on the first day of each cycle (Day 1) for up to 6 doses. Each cycle has 28 days. Paclitaxel will be given through a vein in the arm on the 1st, 8th, and 15th day of each cycle (Days 1, 8, and 15). See the study calendar for more information.

  There will be about 35 people in this group.

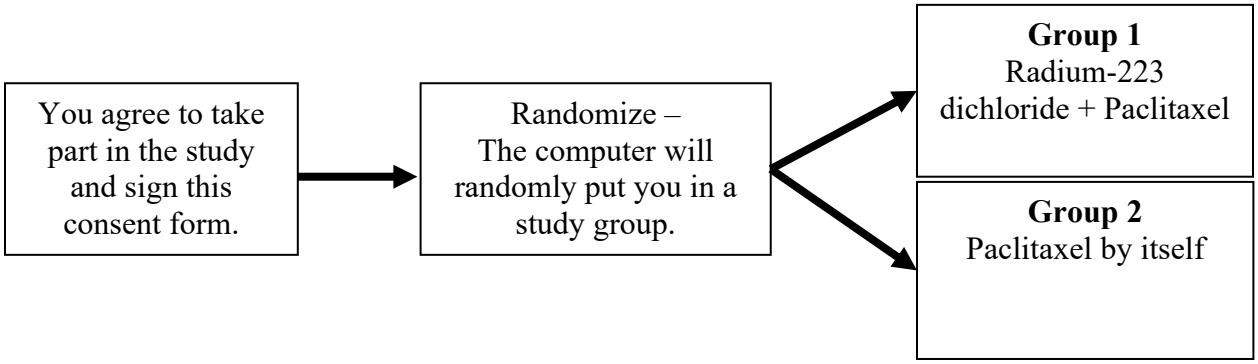
- **Group 2**

  If you are in this group, you will get paclitaxel through a vein in the arm on the 1st, 8th, and 15th day of each cycle (Days 1, 8, and 15). Each cycle lasts 28 days. See the study calendar for more information.

  There will be about 35 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- An ECG before you begin the study. Additional ECGs will be done if your doctor thinks it is necessary.
- Blood counts done before each dose of paclitaxel.
- Tests to measure how well your blood clots.

- CT and bone scans performed every 8 weeks until documentation of progression, initiation of other cancer therapy, or withdrawal from study. After 6 cycles of study therapy, scans may be every 8-12 weeks.
- Blood tests to measure bone health on Day 1 of every cycle and off-study (30 days after treatment ends).

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

1. Research blood test (2 teaspoons) on Day 1 of Cycles 1 through 6 and off-study (30 days after treatment ends). This blood sample will be used to measure the levels of bone proteins in your blood. The change in the levels of this will be looked at to see if they are related to your response to the study drugs. This is a required test.
2. Research blood test (2 teaspoons) on Day 1 (only Cycle 1). This sample will be used for measuring cells and proteins related to your immune system. This is a required test.

You and your study doctor will not get the results of these tests.

Your study doctor will need to use some of the tissue left over from your previous biopsy or surgery when you were diagnosed with breast cancer. This sample is required as part of the study. Researchers will use this sample to obtain genetic material (DNA and RNA) from your tumor tissue and identify changes in tumor DNA and RNA from these samples using 'sequencing' technology. You and your study doctor will not get the results of this testing.

Blood samples will also be taken for the study. The blood sample will be collected before you begin the study drug. These samples are a required part of the study. Researchers will use this sample to obtain tumor genetic material (DNA and RNA) from your blood samples and identify changes in tumor DNA and RNA from these samples using 'sequencing' technology. You and your study doctor will not get the results of this testing. Results from genetic testing will not be a part of your medical records. See "Who will see my medical information?" for laws and risks in protecting your genetic information.

If there is not enough tissue left over from your previous biopsy, your study doctor will need to do another biopsy to get this tissue prior to start of treatment on this trial. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer.

You may also participate in optional surveys about symptoms occurring during the course of this study. Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out this form at 32 times:

- Weekly for 28 weeks(cycles 1-7).

- Once a month for the next 4 months (cycles 8-11).

Each form will take about 5-10 minutes to complete. The forms will ask about things like pain, diarrhea, tiredness, and constipation. You don't have to answer any question that makes you feel uncomfortable.

A patient study calendar is attached at the end of this document. It shows how often these tests will be done.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer at shrinking or controlling your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 6 months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Genetic Testing Risks

The genetic test used in this study will test your tumor and normal tissue for genetic changes. Changes found in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your doctor will talk with you about what testing your normal tissue may mean for you and your family. He or she also may suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for any genetic tests and visits to a genetic counselor done outside of this study.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

If there is any leftover specimen, it may be stored for future research (biobanking). This will be discussed in the section under "Optional studies".

Blood Draw Risks

Some of the risks from drawing blood from your arm may include pain, bruising, light-headedness, and rarely, infection. For most people, needle punctures to get blood samples do not cause any serious harm. Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

If there is any leftover specimen, it may be stored for future research (biobanking). This will be discussed in the section under "Optional studies".

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Paclitaxel (Table Version Date: September 26, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, more than 20 and up to 100 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Pain • Sores in mouth which may cause difficulty swallowing • Diarrhea, nausea, vomiting • Muscle weakness • Numbness, tingling or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, from 4 to 20 may have:
• Abnormal heartbeat • Blood clot which may cause swelling, pain, shortness of breath • Damage to the lungs which may cause shortness of breath

RARE, AND SERIOUS In 100 people receiving Paclitaxel, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or a hole in the bowels which may cause pain or that may require surgery • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

In addition to the side effects listed above for Group 1 and Group 2, people in Group 1 may also have some of the following side effects from Radium-223 dichloride.

Possible Side Effects of Radium-223 dichloride (Table Version Date: December 27, 2018)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radium-223 dichloride (BAY 88-8223) from 4 to 20 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, nausea, vomiting • Swelling of arms, legs • Tiredness • Bruising, bleeding • Loss of appetite • Pain in bone

RARE, AND SERIOUS In 100 people receiving radium-223 dichloride (BAY 88-8223), 3 or fewer may have:
• Swelling and redness at the site of the medication injection • Infection, especially when white blood cell count is low

Additional Drug Risks

The study drug could interact with other drugs. Your study doctor will give you a clinical study wallet card that lists the study drugs. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Imaging Risks

The CT and bone scans that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

Other Risks

Radium-223 dichloride, an alpha particle-emitting pharmaceutical, is a radioactive therapeutic agent. Though the external radiation exposure associated with Radium-223 dichloride is low, care must be used to keep body fluids from coming in contact with family members or caregivers. Use disposable gloves when wiping up blood, urine, stools, or vomit, or when handling stained clothes. Clothing soiled with Radium-223 dichloride or patient fecal matter or urine should be washed promptly and separately from other clothing. Use the same toilet each time you use the bathroom in your home, and if possible, use a different toilet than other members of your household. Sit down on the toilet to urinate to keep urine from splashing or spraying. Please follow these guidelines for at least 7 days after each Radium-223 dichloride

treatment. Flush the toilet a few times after each use. Contact your health care team with questions you may have related to radiation exposure with this drug.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

1. Keep your study appointments.
2. Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 6 months after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

1. the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
2. the costs of getting the drugs ready and giving it to you.
3. your insurance co-pays and deductibles.
4. the blood tests to measure bone health on Day 1 of every cycle and off-study (30 days after treatment ends).

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

1. Research blood testing
2. Collection of tissue from archived sample or fresh biopsy

You or your insurance provider will not have to pay for the Radium-223 dichloride while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

1. Have more travel costs.
2. Need to take more time off work.
3. Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future. This would include any organization helping the company with the study.

- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional surveys about symptoms occurring during the course of this study

If you agree to participate, you will be asked to respond to a series of questions about your symptoms weekly for 28 weeks (Cycles 1-7) and then once a month for the next four months (Cycles 8-11). These surveys will be collected electronically through an app and will take about 5-10 minutes to complete.

Your Android or Apple mobile device (phone or tablet) or if available, a tablet provided at your health care clinic, will be used to enter your answers to the survey questions. Not all clinics have a tablet at their site. The use of your own electronic device on a cellular network may result in a nominal cost to your data plan. Regardless of the device you use, your answers and personal information will not be stored on the device. Your survey answers will be sent to the research database and will be kept private in the same way listed in the earlier section about who will see your medical records. Your e-mail address will only be used for this survey study and will not be used for mail or marketing purposes.

If you need help using the survey application on your phone or tablet, ask for help at your study site. You don't have to answer any question that makes you feel uncomfortable. Someone may help you enter your answers in the device if you need.

Since this is a research survey, the responses you provide will not be shared with your doctor. **If you are having any severe symptoms, health issues or other concerns, please be sure to discuss these with your doctor or nurse right away.** At the end of the study, the answers you provided will be used to learn more about how cancer and cancer treatment affects patients, and it may help future patients.

Please mark your answer below: I choose to participate in the symptoms survey.

YES NO

Optional imaging study – dosimetry (SPECT) scans

If you choose to take part in this study, you will have extra scans (dosimetry scans with SPECT). You will have this scan done 3 times during Cycle 1 (4 hours, 24 hours, and 48 hours after the Radium-223 dichloride dose, *i.e*. Days 1, 2 and 4 of Cycle 1). Researchers would use this scan to measure the uptake of radium in the bones as well as other organs of the body. The scan would only be used for research and not to guide your medical care.

If you agree to have this extra scan, it would involve two extra visits (on Days 2 and 4 of Cycle 1). Getting these scans will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body. Ask your study doctor if you would like to learn more about this type of scan.

Please circle your answer: I choose to take part in the imaging study and will have the extra dosimetry scans:

YES NO

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, any leftover tissue or blood sample will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Nationwide Children's Hospital in Columbus, Ohio, and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood and/or tissue samples. This means that:

1. You will not be asked if you agree to take part in the future research studies.
2. You and your study doctor will not be told when or what type of research will be done. You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. Any leftover blood or tumor tissue will be sent to the biobank.
2. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.

- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information. Only your study doctor and a few study researchers will have access to the master list linking the code numbers to names. The biobank and the genomic sequencing laboratory will receive your samples with the following information only: your sample code number; your age, race/ethnicity, and gender; your type of cancer; any previous treatments you received for your cancer; and the treatment you will receive for this current study.
2. Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are. The researchers must be trained in the handling of private information. Any researcher who wants to study your stored samples and genetic information must apply and be approved to do so.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance for exams, tests, and procedures done for research purposes only; these include any new biopsy required, blood draw, DNA/RNA sequencing, biobanking of your specimen(s), and optional imaging studies. You will not be paid for taking

part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I need my tissue or blood samples to be returned?

Tumor tissue or blood samples that remain in the biobank can be returned if needed for medically necessary events or procedures to assure appropriate medical care, such as for DNA or RNA analysis. Specimens may also be returned if tissue is needed to determine eligibility for enrollment in a research protocol or clinical trial. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness.

Tumor tissue or blood samples and genetic material (DNA and RNA) that is no longer in the biobank or that has already been given to or used by researchers cannot be returned. No samples will be returned for matters related to patients needing or wanting genetic testing to determine medically important risks.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Attachment A: Study Calendar for Protocol 10302 Consent Form

	Pre-study	During Treatment												Off-study (30 days after treatment ends)
		Cycle 1				Cycles 2 to 6				Cycle 7 onwards				
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	
Radium-223 dichloride[A]		X				X								
Paclitaxel[B]		X	X	X		X	X	X		X	X	X		
Pre-study procedures including informed consent, demographics, medical history, and height	X													
Concurrent meds	X	X----------X												
Side effects evaluation		X----------X												X
Physical exam, vital signs, weight, and general well-being	X	X				X				X				X
Blood draws for general health status	X	X	X	X		X	X	X		X	X	X		X
Blood draws to measure bone health		X				X				X				X
Blood draws for scientific study	X	X				X								X
Archival tissue sample[G]	X													
Pregnancy test	X													
ECG[I]	X													
Radiologic evaluations (CT of chest, abdomen and pelvis and nuclear medicine bone scan)[H]	X	Performed every 8 weeks during treatment.												X
Dosimetry (SPECT)—optional		X[C]												
Quality of life questionnaires[F]		X	X	X	X	X	X	X	X	X[D]	X[E]	X[E]	X[E]	

A: Only for patients in Group 1. Radium-223 dichloride will be given at the assigned dose intravenously (IV) on Day 1 of Cycles 1-6.
B: Paclitaxel will be given at the assigned dose IV on Days 1, 8, and 15 of a 28-day cycle continuously.
C: At 4, 24, and 48 hours after treatment on Day 1, Cycle 1.
D: Only in Cycles 7-11.
E: Days 8, 15, and 22 of Cycle 7.
F: Quality of life questionnaires are optional.

	Pre-study	During Treatment												Off-study (30 days after treatment ends)
		Cycle 1				Cycles 2 to 6				Cycle 7 onwards				
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	
G: If archival tissue is not available, a fresh biopsy will be requested. H: Scans will be performed every 8 weeks for the first 6 cycles. After the first 6 cycles, scans will be performed every 8 to 12 weeks. I: An ECG will be done pre-study. Additional ECGs will be done if your doctor thinks it is necessary.														