Clinical Trial of a Rapidly Cycling, Non-Cross Reactive Regimen of Approved Therapeutic Agents to Treat Prostate Cancer
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TITLE OF RESEARCH STUDY:

Title: Prostate Cancer Intensive, Non-Cross Reactive Therapy (PRINT) for CRPC

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WHAT IS A RESEARCH STUDY?

A research study is when scientists try to answer a question about something that we don't know enough about. Participating may not help you or others.

People volunteer to be in a research study. The decision about whether or not to take part is totally up to you. You can also agree to take part now and later change your mind. Whatever you decide is okay. It will not affect your ability to get medical care within the Mount Sinai Health System.

Someone will explain this research study to you. Feel free to ask all the questions you want before you decide. Any new information that develops during this research study that might make you change your mind about participating will be given to you promptly.

Basic information about this study will appear on the website http://www.ClinicalTrials.gov. There are a few reasons for this: the National Institutes of Health (NIH) encourages all researchers to post their research; some medical journals only accept articles if the research was posted on the website; and, for research studies the U.S. Food and Drug Administration (FDA) calls "applicable clinical trials" 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.

PURPOSE OF THIS RESEARCH STUDY:

The purpose of this study is to better understand if cycling between different combinations of prostate cancer treatments already approved by the United States Food and Drug Administration (FDA) can help us achieve better long-term control of the disease. While many new prostate cancer drugs have come out in recent years, the way that most oncologists are treating prostate cancer is to stay with one drug until it no longer works, then switch to a different one. This means that once the disease has become resistant to that drug, all subsequent treatments will need to be able to overcome that resistance in order to be effective. It is easier to develop drug resistance to a single drug as compared to a combination of drugs, since the likelihood of cancer cells forming resistance against two or more drugs simultaneously is less. By switching between different combinations of active treatments before prostate cancer has a chance to develop resistance, we hope to be able to have better long-term control of the disease.

Abiraterone acetate (Zytiga), cabazitaxel (Jevtana), enzalutamide (Xtandi), and radium-223 dichloride (Xofigo) have all been FDA approved for the treatment of metastatic prostate cancer that has progressed despite first line androgen deprivation therapy. Carboplatin is a chemotherapy that is considered standard-of-care for the treatment of many different cancers, and has been well studied in prostate cancer. Some studies have been designed to evaluate the effectiveness and safety of using some of these drugs in combinations with each other, but there have been no studies performed looking at the effects of switching between combinations, both good and bad.

You are being given information about becoming a volunteer in a research study. You may qualify to take part in this research study because you have prostate cancer that is no longer controlled by hormonal therapy alone.

In this study you will receive treatment with all of the drugs listed above but in specific two-drug combinations, and in a specific sequence, as detailed below.

Bayer is providing Radium-223 and Sanofi is providing Cabazitaxel. Funds for conducting this research are provided by both Bayer and Sanofi.

LENGTH OF TIME AND NUMBER OF PEOPLE EXPECTED TO PARTICIPATE

Your participation in this research study is expected to last 2 years.

The number of people expected to take part in this research study at the Icahn School of Medicine at Mount Sinai and the Mount Sinai Hospital is 32; Mount Sinai Downtown Chelsea Center 8. The total number of people expected to take part and receive treatment on this research study is 40.

DESCRIPTION OF WHAT'S INVOLVED:

If you agree to participate in this research study, the following information describes what may be involved.

This is a research study that will be conducted by the Icahn School of Medicine at Mount Sinai at Mount Sinai Hospital, Mount Sinai Downtown Chelsea Center, and Mount Sinai West. Nearly all of

the research studies will take place at the cancer center where you see your oncologist. You may have one additional blood test that will be analyzed by an outside laboratory that we will be partnering with (Epic Sciences, 9381 Judicial Drive, Suite 200, San Diego, CA 92121).

We will review labs and radiology imaging to see if you are eligible for the study. All parts of this evaluation have to be performed no longer than 8 weeks before starting on the study. If you are eligible and consent to the study, you will be asked to return to the clinic for your first study visit. During this visit, the following procedures will take place to establish your baseline status, your study doctor can give you more details about these tests:

- Complete medical history will be collected including information on your general health, past surgeries and past treatments for prostate cancer and medications that you are taking (over the counter medications, herbal remedies, vitamins, and supplements). (This procedure is considered standard of care)
- A complete physical examination including vital signs (blood pressure, heart rate, and temperature), height and weight. (This procedure is considered standard of care)
- To evaluate your disease you will undergo the following imaging studies (This procedure is considered standard of care):
    - Computed Tomography (CT) scan – this test uses x-rays to look at tumors inside the body. The CT scanner is typically a large, box like machine with a hole, or short tunnel, in the center. You will lie on a narrow examination table that slides into and out of this tunnel. The technologist begins by positioning you on the CT examination table, usually lying flat on your back or possibly on your side or on your stomach. Straps and pillows may be used to help you maintain the correct position and to hold still during the exam. A CT scan takes approximately 30 minutes. A contrast agent is a dye that mixes with your blood to help make the images taken by the CT. You will receive a contrast agent, such as iodine, by an IV placed in your arm.
    - Bone scan – this test requires a radioactive tracer substance to be injected into a vein in the arm, and then travels through the bloodstream and collects in your bones. A special camera inside a machine is then used to take images of your bones.
- Electrocardiogram (ECG) to measure the electrical activity of your heart. For this test, you will be asked to lie down while 12 sticky pads are affixed to each of your arms and legs and to your chest. The ECG will last about 20 minutes. (This procedure is considered standard of care)
- Laboratory (blood) tests (This procedure is considered standard of care):
    - Hematology and chemistry analysis to evaluate how well your liver, kidneys, and other organs are working (8ml or 1.5 teaspoons of blood will be taken)
    - Male hormone levels (Testosterone) and prostate-specific antigen (PSA) (5ml or 1 teaspoon of blood will be taken)
- Research (blood) tests (These procedures are research specific, and are required as part of

the study):

- A blood test to look at your genes and how they relate to prostate cancer (10 ml or 2.5 teaspoons of blood will be taken). This blood will be stored for future analysis.
- A blood test to look for the presence of a specific mutation in prostate cancer cells that travel in the bloodstreams (10 ml or 2.5 teaspoons of blood will be taken). This blood sample will be analyzed by the laboratory right away.
- A tube of blood (10 ml or 2.5 teaspoons of blood will be taken) will be drawn and stored in a Streck Cell-Free tube for future studies only if the external laboratory that processes this particular blood sample is ready to receive it. If not, this tube of blood will not be drawn.
- These results will not be shared with you because they are preliminary results intended for research purposes only. They are not intended to manage or improve your healthcare.

Our treatment regimen consists of three treatment modules that last 12 weeks each. Everyone who participates in the study will go through all three modules in sequential order. The treatment drugs (abiraterone acetate, cabazitaxel, carboplatin, enzalutamide, radium-223) and supportive drugs (prednisone, pegfilgrastim) that we are using in this study have all been well studied in advanced prostate cancer. You will be receiving each drug at their approved dosing.

The cancer treatments, lab tests, and imaging studies that you will receive within each module is detailed below:

	Module 1 (12 weeks)**			**Module 2** (12 weeks)**								**Module 3** (12 weeks)**		
	D1	**D29**	**D57**	**D1**	**D2**	**D22**	**D23**	**D43**	**D44**	**D64**	**D65**	**D1**	**D29**	**D57**
Abiraterone	daily													
Prednisone	daily													
Cabazitaxel				x		x		x		x				
Carboplatin				x		x		x		x				
Pegfilgrastim					x		x		x		x			
Prednisone				daily										
Enzalutamide												daily		
Radium-223*												x	x	x

* only in patients with known bone metastases

** deviation from schedule of ± 5 days allowed for IV therapies

Module 1 (12 weeks):

1. Abiraterone acetate 1000 mg (4 tablets of 250 mg each) by mouth once a day. No food should be taken at least 2 hours before and 1 hour after taking abiraterone.
2. Prednisone 5 mg (1 tablet of 5 mg) by mouth two times a day

During this module, you will have blood draws every 2 weeks for the first 4 weeks, then every 4 weeks thereafter. Follow up clinic visits will be scheduled for every 4 weeks during this first treatment module. At the end of the 12 week treatment module, you will receive a CT scan and bone scan.

At the end of this module, we will be able to determine whether or not your disease is responding to treatment with abiraterone acetate. However, regardless of the type of response that you are having to these medications, we will be switching you to the treatment drugs in module 2 (below). This switch in treatment is by design and is the novel approach that our clinical trial is studying.

Module 2 (12 weeks):

1. Cabazitaxel intravenously every 3 weeks
2. Carboplatin intravenously every 3 weeks
3. Pegfilgrastim by injection under the skin every 3 weeks
4. Prednisone 5 mg (1 tablet of 5 mg) by mouth two times a day

During this module, you will have office visits and blood draws every 3 weeks. At the end of the 12 weeks, you will receive a CT scan and bone scan. The use of cabazitaxel and carboplatin in combination has been studied in phase II clinical trials and has been demonstrated to have acceptable and manageable side effects.

At the end of this module, we will be able to determine whether or not your disease is responding to treatment with the combination of cabazitaxel and carboplatin. However, regardless of the type of response that you are having to these medications, we will be switching you to the treatment drugs in module 3 (below). This switch in treatment is by design and is the novel approach that our clinical trial is studying.

Module 3 (12 weeks):

1. Enzalutamide 160 mg (4 tablets of 40 mg each) by mouth once a day
2. Radium-223 dichloride intravenously every 4 weeks

During this module, you will have blood draws every 2 weeks for the first 4 weeks, then every 4 weeks thereafter. Follow up clinic visits will be scheduled every 4 weeks during this third treatment module. At the end of the 12 weeks, you will receive a CT scan and bone scan.

After the completion of all three sequential modules of treatment, you will stop all prostate cancer treatments with the exception of a GnRH (gonadotropin releasing hormone) agonist or antagonist (e.g., leuprolide, goserelin, degarelix) and we will carefully monitor for any signs of prostate cancer progression though office visits every 4 weeks, checking blood work every 4 weeks, and repeating CT and bone scans every 12 weeks, until you have completed the first 12 weeks of surveillance. After the first 12 weeks of surveillance, it will be arranged for you to have blood work checked every 4 weeks, but office visits with the doctor will be every 12 weeks. CT and bone scans will still be repeated every 12 weeks while you remain on surveillance.

Your study doctor will continue to follow with you on the study for up to 24 months so that he/she may follow the progression of disease.

If there is evidence of disease progression during the follow up period, your study doctor will decide with you what would be the best way to treat your disease. Any of the drugs that you have received as part of the study will still be available to you for use. At this time, the schedule of office visits, blood work, CT and bone scans, and treatment visits will then no longer be decided by the clinical trial, but will be arranged for you by your treating doctor based on what type of treatment is decided on next.

Each office visit with your study doctor will usually take about an hour, and chemotherapy treatment sessions will be about 2 hours each. Each time we draw blood, approximately 50 mL (10 tsp) will be taken.

The chart below shows you what procedures will be done during the study.

	Baseline	**Treatment**			**Post-Treatment Surveillance**
		Module 1	**Module 2**	**Module 3**	
Informed Consent	Once				
Medical History	Once				
Physical Examination	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks for the first 12 weeks, then every 12 weeks

					thereafter*
Vital Signs/Weight	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks for the first 12 weeks, then every 12 weeks thereafter*
Performance Status	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks for the first 12 weeks, then every 12 weeks thereafter*
Complete blood count with differential	Once	Every 2 weeks for the first 4 weeks, then every 4 weeks thereafter	Every 3 weeks	Every 2 weeks for the first 4 weeks, then every 4 weeks thereafter	Every 4 weeks*
Blood test chemistries (CMP and LDH)	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks*
PSA (prostate specific antigen)	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks*
Testosterone	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks*
Electrocardiogram	Once	Every 4 weeks			
Adverse Event Monitoring	Once	Every 4 weeks	Every 3 weeks	Every 4 weeks	Every 4 weeks for the first 12 weeks
CT scan of chest, abdomen, and pelvis	Once	Every 12 weeks	Every 12 weeks	Every 12 weeks	Every 12 weeks*
Bone Scan	Once	Every 12	Every 12	Every 12	Every 12

		weeks	weeks	weeks	weeks*
PAXgene Blood RNA tube (Research test)	None	At the start of the module	At the start of the module	At the start of the module	At the start of surveillance, and again in 12 weeks
Streck Cell-Free DNA tube (Research test)**	None	At the start of the module**	At the start of the module**	At the start of the module**	At the start of surveillance**

*Until there is evidence of disease progression, after which the schedule of office visits, blood work, CT and bone scans, and treatment visits will be decided upon by your treating doctor.

**Only if the external laboratory that performs this test is ready to receive this specimen. If not, this tube will not be drawn.

Since you are participating in a study that involves drugs or treatment with potential risks to a developing fetus, it is recommended that you use a condom and not father a child or donate sperm while you are taking the study drug. Also, it is recommended that you use a condom and not father a child and/or donate sperm for 90 days after you stop taking the study drug. This is because levels of the study drug may be present in the sperm and/or seminal fluid even after you stop taking the study drug. Continuing to use a condom and not donating sperm during this 90 day period may allow time for any study drug that is still present in sperm and/or seminal fluid to be eliminated from your body before you attempt to father a child or donate sperm. You are encouraged to tell your female partner(s) and/or their doctor(s) that you are participating in a clinical trial.

Research blood studies

There are research blood tests that are being performed as part of the study. These tests are being performed to see if certain expressions of genes in your blood, or in the prostate cancer tumor cells that circulate in the bloodstream, have an effect on how your body and prostate cancer responds to certain prostate cancer treatments. These labs will be collected in special study tubes called PAXgene Blood RNA tubes and Streck Cell-Free DNA blood collection tubes.

In some cases, your sample will be destroyed and investigator will only keep study information collected/generated up to that point. There will be no direct benefit to you by taking part in this genetic research.

These results will not be shared with you because they are preliminary results intended for research purposes only. They are not intended to manage or improve your healthcare.

The physical risks and discomforts of giving this blood sample are the same as those for any blood sample taken from a vein. You may feel faint, experience mild pain, bruising, irritation or redness at

the site of puncture. In rare instances, you may develop an infection.

The investigator has taken reasonable steps to keep your research information confidential. However, confidentiality cannot be guaranteed and there is a possibility that this could affect your insurance or employment. To protect your privacy, your samples will be coded and stored. Coding means that your specimens will be assigned an identifier such as a number so that the laboratory personnel analyzing your specimens will not know your identity. Your consent will limit the usage of your samples to the two tests described above. In addition, your consent limits the storage time of your coded samples to a period of 15 years, at which time your samples will be destroyed. The data that result from your samples may be stored for a time period of 15 years or even longer, if required by regulatory authorities. It may be necessary to send your coded samples and data to other countries and/or cooperating laboratories for analyses.

If there is still any blood remaining after these two required tests, the researchers would like to ask your permission to keep blood specimens collected from you during this study to use them in future research studies. They would also like to know your wishes about how they might use your specimens in future research studies. You should also know that it is possible that products may someday be developed with the help of your specimens, and that you will not receive any financial benefit that might come from the research.

(1) Will you allow the researchers to store your specimens to use in future research studies? Please initial your choice:

Yes_____ No_____ If no, please stop here. If yes, please continue to the next question.

(2) Do you give the researchers permission to **contact you** in the future to collect additional information about you, discuss how your specimens might be used, or to discuss possible participation in another research project? Please initial your choice:

Yes_____ No_____

(3) Do you give the researchers permission to keep the specimens indefinitely and use them for future studies that are **directly related** to the purpose of the current study? Please initial your choice:

Yes_____ No_____

(4) Do you give the researchers permission to keep the specimens indefinitely and use them for future studies that are **not related** to the purpose of the current study (for example, a different area of research)? Please initial your choice:

Yes_____ No_____

(a) If the future research in a different area can be done without having to know that the specimens came from you personally, that will be done.

(b) If the future research in a different area requires that it is known specifically who the specimens came from, then one of the following will be done:

(i) If you allowed the researchers to contact you in the future, they will be able to contact you to explain why your specimen is needed and what will be done with it. Your permission will be asked to use your specimens in that research project.

(ii) If you do not give permission to be contacted in the future, or if it is found that contacting you is not practical, for example, because you have moved, your specimens may still be used. Either all links to your identity will be removed from the specimens, or an Institutional Review Board will be asked for permission to use the specimens linked to your identity. The Institutional Review Board (IRB) is a committee of doctors and scientists and non-scientists and people not associated with this hospital or medical school whose job it is to protect people who participate in research. The IRB can give permission for researchers to use and share health information connected to specimens that are linked to people's identities, but only if it determines that doing this will not be more than a minimal risk to people or their privacy.

(5) Do you give permission to have portions of the specimens **given to other researchers** at Mount Sinai or other institutions for use in research that is either related or not related to the purpose of this study? Please initial your choice:

Yes_____ No_____

YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study you will be responsible for the following things: complying with requirements of the study, taking prescribed medications, use of birth control as stated below, and avoidance of certain medications and attendance at study visits.

If you have a partner that is able to have children, you must be willing to use a barrier form of birth control during the study and for 1 week after you have taken the last dose of the study drug.

COSTS OR PAYMENTS THAT MAY RESULT FROM PARTICIPATION:

Taking part in this research study may lead to added costs to you. You or your insurance company will be responsible for the costs of all items and services during the research study, which you would have received for your condition if you were not enrolled in this research study. You or your insurance company will also be responsible for the costs of all services that occur during the research study that your physician believes are medically necessary to treat you. You or your insurance company will not be responsible for the costs of the items and services associated with this research study, which are provided to you only for research purposes and not to treat your condition. Some of the medications used in this study will need to be obtained through your insurance and you will be responsible for your prescription copayments.

You will not be paid for participating in this research study. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

POSSIBLE BENEFITS:

It is important to know that you may not get any benefit from taking part in this research. Others may not benefit either. However, possible benefits may be improved long-term control of your prostate cancer. Your disease may worsen while on this study due to the nature of the disease itself. Future subjects with cancer may benefit from the results of this study.

REASONABLY FORESEEABLE RISKS AND DISCOMFORTS:

The side effects of each of the treatment drugs used in this study have been well studied in large clinical trials. You may have side effects from taking the study treatment (abiraterone acetate, radium-223 dichloride, cabazitaxel, carboplatin, enzalutamide, prednisone, pegfilgrastim). Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team could give you medicines to treat the side effects. Many side effects caused by study medication may go away soon after you stop taking the study treatment. In some cases side effects can be serious, long lasting, or may never go away. It is not possible to tell which side effect will affect you or how mild or severe the side effect might become. We can only tell you what other people have experienced. Please talk with your study doctor about these side effects.

You should tell your study doctor about any side effects, problems or unusual experiences that you have while taking part in this study. This may decrease the chance that the side effects continue or become worse. Sometimes there are other medications that your doctor can give you to make the side effects better or make you more comfortable. If severe side effects do develop, you and your doctor may decide it is in your best interest to stop taking part in the study.

In patients with prostate cancer, it is often difficult to know if side effects after starting a new medication are due to the medication versus symptoms of the underlying cancer itself.

Risks Associated with Abiraterone

In clinical trials in which some patients were given abiraterone and other patients were given a placebo, some side effects occurred only slightly more commonly with abiraterone compared with placebo. At present, known side effects occurring in patients taking abiraterone include:

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- peripheral edema (swelling of the legs as a result of the body keeping too much fluid)
- hypokalaemia *(*low blood potassium, a mineral that helps regulate heart rate/function, fluid balance in the body and is needed for adequate body function)
- hypertension (high blood pressure)
- urinary tract infection
- fatigue (feeling tired)
- muscle or joint pain or stiffness
- constipation
- diarrhea
- nausea
- poor appetite
- elevated blood sugar
- urinary tract infection
- shortness of breath or cough
- hot flashes

Common (≥ 1/100 to < 1/10) [*may occur between 1 and 9 subjects in 100]*

- alanine aminotransferase increased (an enzyme that measures the function of the liver)
- aspartate aminotransferase increased (an enzyme in the blood that measures the function of the liver)
- hypertriglyceridaemia (high blood levels of triglycerides, fatty molecule)
- cardiac failure (decreased function of the heart)
- congestive heart failure (a weakness of the heart that leads to a buildup of fluid in the lungs and surrounding body tissues)
- left ventricular dysfunction (inefficient pumping of the left side of the heart)
- ejection fraction decreased (inability of the heart to pump blood)
- angina pectoris (chest pain)
- arrhythmia (changes in the rhythm of the heart)
- atrial fibrillation (a fast and irregular heartbeat)
- tachycardia (rapid heartbeats)
- fractures (a break in the bone)
- dyspepsia (indigestion)
- hematuria (presence of blood in the urine)

- hyponatremia (low blood sodium)
- hypomagnesemia (low blood magnesium)
- hypocalcemia (low blood calcium)
- hypophosphatemia (low blood phosphorus)
- hypoalbuminemia (low blood albumin)
- pneumonia (infection of the lungs)
- sinusitis (infection of the sinuses)
- other infections
- creatinine increased (a protein that measures function of the kidneys)
- rash

Uncommon (≥ 1/1,000 to < 1/100) [*may occur between 1 and 9 subjects in 1000]*

- adrenal insufficiency (disorder that occurs when the adrenal glands do not produce enough of certain hormones/ adrenal glands, located above the kidneys, do not produce adequate amounts of steroid hormones or if you stop your prednisone/prednisolone suddenly)

Rare (Less than <.1% chance that this will happen)

- non-infectious pneumonitis (swelling and irritation of the lung)

Risks Associated with Radium-223

In clinical trials in which some patients were given radium-223 and other patients were given a placebo, some side effects occurred only slightly more commonly with radium-223 compared with placebo. At present, known side effects occurring in patients taking radium-223 include:

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- Peripheral edema (swelling of the legs as a result of the body keeping too much fluid)
- Nausea
- Diarrhea
- Vomiting
- Anemia (decreased red blood cell count)
- Lymphocytopenia (decreased number of lymphocytes, a particular type of white blood cell)
- Leukopenia (decreased white blood cell count)
- Thrombocytopenia (decreased platelet count)
- Neutropenia (decreased number of neutrophils, a particular type of white blood cell)

Common (≥ 1/100 to < 1/10) [*may occur between 1 and 9 subjects in 100]*

- Dehydration
- Pancytopenia (decreased number of white blood cells, red blood cells, and platelets)
- Injection site reactions (swelling, pain, or redness of the skin where the drug is given)

- Renal failure/insufficiency (decreased kidney functioning)

Rare (Less than <0.1% chance that this will happen)

- Aplastic anemia (damage to the blood stem cells causing the inability to produce white blood cells, red blood cells, and platelets)

Risks Associated with Enzalutamide

In clinical trials in which some patients were given enzalutamide and other patients were given a placebo, some side effects occurred only slightly more commonly with enzalutamide compared with placebo. At present, known side effects occurring in patients taking enzalutamide include:

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- Peripheral edema (swelling of the legs as a result of the body keeping too much fluid)
- Hypertension (high blood pressure)
- Fatigue (tiredness)
- Falling
- Headache
- Dizziness
- Hot flash
- Weight loss
- Constipation
- Diarrhea
- Decreased appetite
- Neutropenia (decreased number of neutrophils, a particular type of white blood cell)
- Weakness
- Back pain
- Arthralgia (joint pain)
- Muscle or skeletal pain
- Upper respiratory tract infection
- Dyspnea (shortness of breath)

Common (≥ 1/100 to < 1/10) [*may occur between 1 and 9 subjects in 100]*

- Insomnia (difficulty sleeping)
- Anxiety
- Paresthesia (abnormal sensation, typically pins and needles)
- Cauda equina syndrome (compression of the spinal cord nerve roots by a vertebral fracture or tumor)
- Spinal cord compression (compression of the spinal cord by a vertebral fracture or tumor)
- Altered mental status (confusion or delirium)

- Hypoesthesia (decreased sense of touch or sensation)
- Hallucination
- Restless leg syndrome
- Pruritus (itchiness)
- Xeroderma (dry skin)
- Gynecomastia (breasts enlargement)
- Dysgeusia (changes to taste)
- Hematuria (blood in urine)
- Pollakiuria (increased urinary frequency)
- Thrombocytopenia (decreased platelet count)
- Increased serum bilirubin (an enzyme in the blood that measures the function of the liver)
- Infection
- Bone fracture (break)
- Stiffness
- Lower respiratory tract infection
- Epistaxis (nosebleed)

Rare (Less than <0.1% chance that this will happen)

- Reversible posterior leukoencephalopathy syndrome (a syndrome characterized by headache, confusion, seizure, and visual loss, associated with characteristic findings of swelling seen on MRI of the brain)
- Seizure

Risks Associated with Cabazitaxel

Known side effects from clinical trials in which patients were given cabazitaxel include:

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- Fatigue (tiredness)
- Fever
- Diarrhea
- Nausea
- Vomiting
- Constipation
- Abdominal pain
- Anorexia (decreased appetite)
- Taste alteration (changes to taste)
- Anemia (decreased red blood cell count)
- Leukopenia (decreased white blood cell count)

- Neutropenia (decreased number of neutrophils, a particular type of white blood cell)
- Thrombocytopenia (decreased platelet count)
- Weakness
- Back pain
- Peripheral neuropathy (damage to small nerves of hands and feet causing sensation of weakness, numbness, and pain)
- Arthralgia (joint pain)
- Hematuria (blood in urine)
- Dyspnea (shortness of breath)
- Cough

Common (≥ 1/100 to < 1/10) [*may occur between 1 and 9 subjects in 100]*

- Peripheral edema (swelling of the legs as a result of the body keeping too much fluid)
- Arrhythmia (abnormal heart rhythm)
- Hypotension (low blood pressure)
- Dizziness
- Headache
- Pain
- Alopecia (loss of hair)
- Dehydration
- Dyspepsia (upset stomach)
- Weight loss
- Mucosal inflammation (inflammation of the inside lining of the gastrointestinal tract)
- Urinary tract infection
- Dysuria (discomfort with urination)
- Neutropenic fever (fever caused by infection due to having a suppressed immune system)
- Alanine aminotransferase increased (an enzyme in the blood that measures the function of the liver)
- Aspartate aminotransferase increased (an enzyme in the blood that measures the function of the liver)
- Bilirubin increased (an enzyme in the blood that measures the function of the liver)
- Muscle spasm

Rare (Less than <0.1% chance that this will happen)

- Colitis (inflammation of the colon)
- Electrolyte imbalance (increase or decrease of electrolytes found in the blood, such as sodium, chloride, magnesium, potassium, and calcium)
- Enterocolitis (inflammation of the stomach and colon)
- Gastritis (inflammation of the stomach)

- Gastrointestinal hemorrhage (bleeding from the gastrointestinal tract)
- Gastrointestinal perforation (a hole forming in the wall of the gastrointestinal tract)
- Hypersensitivity (allergic-type reactions, such as rash, redness, low blood pressure, and difficulty breathing)
- Intestinal obstruction (blockage of the gastrointestinal tract)
- Neutropenic enterocolitis (inflammation of the stomach and colon caused by suppressed immune system)
- Renal (kidney) failure
- Sepsis (severe infection)

Risks Associated with Carboplatin

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- Pain
- Hyponatremia (low blood sodium, a mineral that helps regulate heart rate/function, fluid balance in the body, and is needed for adequate body function)
- Hypomagnesemia (low blood magnesium, a mineral that helps regulate heart rate/function, fluid balance in the body and is needed for adequate body function)
- Hypocalcemia (low blood calcium, a mineral that helps regulate heart rate/function, fluid balance in the body, and is needed for adequate body function)
- Hypokalemia (low blood potassium, a mineral that helps regulate heart rate/function, fluid balance in the body, and is needed for adequate body function)
- Vomiting
- Abdominal pain
- Nausea
- Bone marrow depression (decreased ability for the bone marrow to produce new white blood cells, red blood cells, and platelets)
- Leukopenia (decreased white blood cell count)
- Neutropenia (decreased number of neutrophils, a particular type of white blood cell)
- Thrombocytopenia (decreased platelet count)
- Increased serum alkaline phosphatase (an enzyme in the blood that measures the function of the liver)
- Increased aspartate aminotransferase (an enzyme in the blood that measures the function of the liver)
- Hypersensitivity (allergic-type reactions, such as rash, redness, low blood pressure, and difficulty breathing)
- Weakness
- Decreased creatinine clearance (decreased kidney function)

Common (≥ 1/100 to < 1/10) [*may occur between 1 and 9 subjects in 100]*

- Peripheral neuropathy
- Neurotoxicity
- Alopecia (loss of hair)
- Constipation
- Diarrhea
- Dysgeusia (changes to taste)
- Mucositis (inflammation to lining of mouth and throat)
- Stomatitis (inflammation of mouth and lips)
- Bleeding complications
- Hemorrhage (bleeding)
- Increased serum bilirubin (an enzyme in the blood that measures the function of the liver)
- Infection
- Visual disturbance (changes to vision)
- Ototoxicity (changes to hearing such as decreased hearing or ringing in ears)

Rare (Less than <0.1% chance that this will happen)

- Anaphylaxis (severe allergic reaction)

Risks Associated with Prednisone

- High blood pressure
- High blood glucose (sugar) level
- Fluid retention
- Increased intra-ocular (eye) pressure or glaucoma
- Menstrual irregularities
- Worsening of pre-existing abnormal thyroid hormone levels
- Stomach bleeding, indigestion
- Muscle weakness and muscle loss
- Osteoporosis
- Easy bruising
- Thin skin
- Weakens body's ability to fight off infection, and can make infections hard to diagnose or treat
- Headache
- Mood swings
- Personality changes
- Severe depression
- Increased intra-cranial pressure (pressure increased in head/skull)
- Cataracts

- Vertigo
- Hallucinations
- Congestive heart failure (worsening heart function) in patients with pre-existing heart disease
- Muscle tears or bone fractures
- Insomnia (wakefulness)
- Cushing's syndrome includes weight gain, a "moon-faced" appearance, thin fragile skin, muscle weakness, brittle bones and purplish stripe marks on the skin.
- Adrenal insufficiency (loss of function of adrenal glands that normally help maintain blood pressure, balance minerals and fluid in your body)
- Sudden stoppage of prednisone/prednisolone, may lead to tiredness, very low blood pressure, very low blood sugar, and abnormalities of the minerals in bloodstream.

Risks Associated with Pegfilgrastim

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- Ostealgia (bone pain)

Common (≥ 1/100 to < 1/10) [*may occur between 1 and 9 subjects in 100]*

- Limb pain

Rare (Less than <0.1% chance that this will happen)

- Splenic rupture (medical emergency where spleen swells and bursts)
- Acute respiratory distress syndrome (life threatening lung condition that prevents enough oxygen from getting to the lungs and into the blood)
- Anaphylaxis (serious allergic reaction)
- Leukocytosis (increased white blood cell count)
- Fever
- Flushing
- Polyarthralgia (joint pain)
- Chest pain
- Musculoskeletal pain (muscle and skeletal pain)
- Urticaria (hives)
- Weakness
- Splenomegaly (enlarged spleen)
- Allergies to acrylics. (the on-body injector for pegfilgrastim uses acrylic adhesive)
- Glomerulonephritis (inflammation of the kidney)
- Capillary leak syndrome (rare disorder characterized by leakage of plasma and other blood components from blood vessels into neighboring body cavities and muscles)
- Severe sickle cell crisis (for people with a history of sickle cell disease, this medication can cause severe and sometimes fatal sickle cell crises)

- Injection site reaction (redness, irritation, or swelling at the site of injection)
- Periorbital edema (swelling or retention of water around the eyes)
- Sweet's syndrome (rare skin condition marked by fever and painful skin lesions that appear mainly on your arms, neck, face and back)

Risks Associated with Imaging Scans

You will have radiation-based procedures or examinations that are part of the regular care for your condition and you will have them whether or not you participate in this research. You will not be exposed to any additional radiation because you are participating in this research.

You will be exposed to radiation from the CT scans and Bone scans, and from the MUGA done to test how well your heart is pumping. The following information will help you understand how much radiation, and the risks from the radiation. Radiation is measured in units called “millisieverts” (mSv.) We are all exposed to radiation on a daily basis from natural sources such as the sun, or artificial sources such as computer screens. This exposure is called “background exposure”. A person living in the US gets 6.2 mSv of background exposure each year. The United States Nuclear Regulatory Commission (NRC) sets recommendations for additional radiation exposure. For the general public, the yearly limit is 1 mSv. For people who work with radiation, such as X-ray technicians, the yearly limit is 50 mSv.

One CT of the chest, abdomen, and pelvis exposes you to 17 mSv of radiation. One bone scan exposes you to 5.3 mSv.

In the first year of the study you will have one CT of the chest, abdomen and pelvis and one bone scan every 3 months. The total exposure from these tests in the first year is 89.2 mSv. In the second year of the study you will have one CT of the chest abdomen and pelvis and one bone scan every 3 months, for a total exposure of 89.2 mSv for the second year.

The radiation exposure for each year of the study is greater than the background exposure and greater than the NRC yearly limits for people who work with radiation (50 mSv). However, the investigators feel that this level or exposure is acceptable because it is no greater than the amount of radiation that you would receive from standard medical monitoring of your condition. The study team will discuss radiation exposure with you.

The study team will always try to minimize your exposure to radiation by whenever possible using tests that involve the least amount of exposure possible. The radiation from the tests and treatments in this study would be in addition to any radiation you might receive from other medical tests or treatments. If you are going to have any other tests or treatments that involve radiation, please inform the study team.

Blood Draws

The risks of having blood drawn include, pain, bruising, and rarely, infection. Blood will be drawn by experienced technicians, and whenever possible it will be obtained at a time when blood is being obtained for other tests your doctor has ordered.

Economic risks

These include having to pay money out of pocket for copayment on certain drugs required for this study, and potentially needing to miss work for study and treatment visits.

Genetic Risks

There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers of over 15 people to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Privacy risks

There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

Unknown Risks

In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

OTHER POSSIBLE OPTIONS TO CONSIDER:

You may decide not to take part in this research study without any penalty. The choice is totally up to you.

Instead of being in this research study, your choices may include:

- Getting treatment or care for your cancer without being in a study.
- Receiving abiraterone (Zytiga) without being in the study. Abiraterone is currently approved by the FDA for patients with metastatic prostate cancer that has progressed despite hormonal therapy.
- Receiving radium-223 dichloride without being in the study. Radium-223 is currently approved by the FDA for patients with prostate cancer with bone metastasis that has progressed despite hormonal therapy
- Receiving enzalutamide (Xtandi) without being in the study. Enzalutamide is currently approved by the FDA for patients with metastatic prostate cancer that has progressed despite hormonal therapy.
- Receiving docetaxel (Taxotere). Docetaxel is a chemotherapy drug approved by the FDA for the treatment of metastatic prostate cancer that has progressed despite hormonal therapy. The risks of treatment are lowering of the blood counts, infection, fatigue, and numbness of the fingers and toes.

- Receiving sipuleucel-T (Provenge). Sipuleucel T is approved by the FDA for metastatic prostate cancer that has progressed despite hormonal therapy. The risks of this treatment are chills, fever, fatigue, nausea, and headahce which usually occur within the first few days of treatment.
- Taking part in another study, if one will become available
- Getting no treatment

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

IN CASE OF INJURY DURING THIS RESEARCH STUDY:

If you are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to you or your insurance in the ordinary manner and you will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance. This does not prevent you from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

If you are injured or become ill from the Study Drug or from one of the Study tests or procedures, you or your insurance company will be billed for the costs of treatment if the injury or illness is due to an underlying medical condition or from the normal progression of your cancer. Bayer and Sanofi, who is providing funding support and study product, will not pay for any costs associated with patient injury/medical costs.

Even if you sign this form, you have not given up any of your legal rights and could choose to file a claim.

ENDING PARTICIPATION IN THE RESEARCH STUDY:

You may stop taking part in this research study at any time without any penalty. This will not affect your ability to receive medical care at any of the Mount Sinai Health System hospitals or to receive any benefits to which you are otherwise entitled.

If you decide to stop being in the research study, please contact the Principal Investigator or the research staff.

If you decide to stop being in the research study, the following may occur: you may stop experiencing benefit from the treatment regimen, and there may be possibility for your disease to progress.

If you stop being in the research study, already collected information may not be removed from the research study database and will continue to be used to complete the research analysis. You may be asked whether the investigator can collect information from your routine medical care. If you agree, this data will be handled the same as research data. Some of the labs drawn as part of the study are used for research, you may be asked whether these labs can still be drawn during routine blood

draws for your ongoing medical care. Samples that have already been collected cannot be withdrawn or destroyed, but are anonymized.

You may also withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, the Principal Investigator for the research study may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from participating in the research study.

Withdrawal without your consent: The study doctor, the sponsor or the institution may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in your best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without your consent. More possible reasons for removal from the study include initiation of other active prostate cancer treatments without study permission.

CONTACT PERSON(S):

If you have any questions, concerns, or complaints at any time about this research, or you think the research has hurt you, please contact the office of the research team and/or the Principal Investigator at phone number: 212-604-6010.

If you experience an emergency during your participation in this research, please call 911 or go to the emergency room.

This research has been reviewed and approved by an Institutional Review Board. You may reach a representative of the Program for Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai at telephone number (212) 824-8200 during standard work hours for any of the reasons listed below. This office will direct your call to the right person within the Mount Sinai Health System:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You are not comfortable talking to the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

DISCLOSURE OF FINANCIAL INTERESTS:

Sometimes, physicians/researchers receive payments for consulting or similar work performed for industry. Effective September 2014 Mount Sinai reviews only payments to an individual totaling more

than $5,000 a year per entity when determining potential conflicts of interest. If you have questions regarding industry relationships, we encourage you to talk your physician/researcher or visit our website at http://icahn.mssm.edu/ where Mount Sinai publicly discloses the industry relationships of our faculty.

Dr. William Oh (a Co-Investigator in this study) receives financial compensation as an advisory board member or consultant for Bayer (a co-sponsor of this study and manufacturer of the study drug Radium-223), Sanofi-Aventis (a co-sponsor of this study and manufacturer of study drug cabazitaxel), and Janssen Biotech, Inc. (manufacturer of the study drug abiraterone).

MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:

As you take part in this research project it will be necessary for the research team and others to use and share some of your private protected health information. Consistent with the federal Health Insurance Portability and Accountability Act (HIPAA), we are asking your permission to receive, use and share that information.

What protected health information is collected and used in this study, and might also be disclosed (shared) with others?

As part of this research project, the research team at the hospital(s) involved in the research will collect your name, address, telephone/fax numbers, birth date, hospital admission or discharge dates, email address, social security number, medical record number, health plan numbers, biometric identifiers, and photographic images. Only if applicable, date of death will be recorded.

The researchers will also get information from your medical records from your outpatient doctors, including your primary care doctor and any specialists you are seeing, and any hospital admissions.

During the study the researchers will gather information by:

- taking a medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.)
- doing a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- completing the tests, procedures, questionnaires and interviews explained in the description section of this consent.
- reviewing genetic tests

Why is your protected health information being used?

Your personal contact information is important to be able to contact you during the study. Your health information and the results of any tests and procedures being collected as part of this research study

will be used for the purpose of this study as explained earlier in this consent form. The results of this study could be published or presented at scientific meetings, lectures, or other events, but would not include any information that would let others know who you are, unless you give separate permission to do so.

The Principal Investigator may also use and share the results of these tests and procedures to treat you in collaboration with others in the Mount Sinai Health System.

The research team and other authorized members of The Mount Sinai Health System ("Mount Sinai") workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements. For example, the School's Program for the Protection of Human Subjects is responsible for overseeing research on human subjects, and may need to see your information. If you receive any payments for taking part in this study, the Mount Sinai Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes. If the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.

Who, outside Mount Sinai, might receive your protected health information?

As part of the study, the Principal Investigator, study team and others in the Mount Sinai workforce may disclose your protected health information, including the results of the research study tests and procedures, to the following people or organizations: (It is possible that there may be changes to the list during this research study; you may request an up-to-date list at any time by contacting the Principal Investigator.)

- Other collaborating research center(s) and their associated research/clinical staff who are working with the investigators on this project: The Icahn School of Medicine at Mount Sinai and the Mount Sinai Hospital, Mount Sinai Beth Israel, and Mount Sinai West
- Research data coordinating office and/or their representative(s) who will be responsible for collecting results and findings from all the centers: Mount Sinai
- The commercial sponsor and/or their representative (who will use the results for submissions to the Food and Drug Administration): Bayer, Sanofi
- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety.
- The United States Food and Drug Administration
- The United States Department of Health and Human Services and the Office of Human Research Protection.

In all disclosures outside of Mount Sinai, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number. The Principal Investigator will ensure that the key to the code will be kept in a locked file, or will be securely stored electronically. The code will not be used to link the information back to

you without your permission, unless the law requires it, or rarely if the Institutional Review Board allows it after determining that there would be minimal risk to your privacy. It is possible that a sponsor or their representatives, a data coordinating office, a contract research organization, may come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally, when applicable, the monitors, auditors, the IRB, the Office of Human Subjects Protection (OHRP) of the Department of Health and Human Services as well as the Food and Drug Administration (FDA) will be granted direct access to your medical records for verification of the research procedures and data. OHRP and FDA are authorized to remove information with identifiers if necessary to complete their task. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

For how long will Mount Sinai be able to use or disclose your protected health information?

Your authorization for use of your protected health information for this specific study does not expire.

Will you be able to access your records?

During your participation in this study, you will have access to your medical record and any study information that is part of that record. The investigator is not required to release to you research information that is not part of your medical record.

Do you need to give us permission to obtain, use or share your health information?

NO! If you decide not to let us obtain, use or share your health information you should not sign this form, and you will not be allowed to volunteer in the research study. If you do not sign, it will not affect your treatment, payment or enrollment in any health plans or affect your eligibility for benefits.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, the Principal Investigator for the research study may still use your protected information that was already collected if that information is necessary to complete the study. Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event (a bad effect) from being in the study. If you withdraw your permission to use your protected health information for research that means you will also be withdrawn from the research study, but standard medical care and any other benefits to which you are entitled will not be affected. You can also tell us you want to withdraw from the research study at any time without canceling the Authorization to use your data.

If you have not already received it, you will also be given The Hospital's Notice of Privacy Practices that contains more information about how The Hospital uses and discloses your protected health information.

It is important for you to understand that once information is disclosed to others outside Mount Sinai, the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, even if your information will no longer be protected by federal regulations,

where possible, Mount Sinai has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If as part of this research project your medical records are being reviewed, or a medical history is being taken, it is possible that HIV-related information may be revealed to the researchers. If that is the case, the following information concerns you. If this research does not involve any review of medical records or questions about your medical history or conditions, then the following section may be ignored.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that the recipient(s) is (are) prohibited from re-disclosing any HIV-related information without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (888) 392-3644 or the New York City Commission on Human Rights at (212) 306-5070. These agencies are responsible for protecting your rights.

Signature Block for Capable Adult

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.

DO NOT SIGN THIS FORM AFTER THIS DATE → [ ]

Signature of subject	Date
Printed name of subject	Time [required if used for FDA documentation purposes]

Person Explaining Study and Obtaining Consent

Signature of person obtaining consent	Date
Printed name of person obtaining consent	Time

Witness Section: For use when a witness is required to observe the consent process,, document below (for example, subject is illiterate or visually impaired, or this accompanies a short form consent):

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	*Date*
Printed name of person witnessing consent process	Time