COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

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

Study Title: A phase I/II clinical trial evaluating the safety and clinical activity of radioiodide (^{131}I-) as a novel targeted therapy for metastatic breast cancer that overexpresses functional Na/I symporter

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Phase I

Invitation to Participate and Description of Project

You are invited to take part in a research study because you have metastatic breast cancer that has gotten worse after you have received treatment with all available Food and Drug Administration approved therapies for breast cancer. The research study will test if radioiodide (known as sodium iodide ^{131}I-), that is approved to treat metastatic thyroid cancer, could be used to treat metastatic breast cancer. The study includes a screening step with a lower dose of radioiodide (known as iodide ^{124}I-) to determine the uptake of iodide into the cancer using an imaging scan. All patients who agree to participate in this study will be screened for iodide uptake but only those who show high levels of uptake during the screening study will receive treatment with iodide ^{131}I- one time. The treatment study is divided into two phases:

- Phase I will test different doses of radioiodide to find the maximum dose that can be safely tolerated by subjects with metastatic breast cancer
- The Phase II portion of the study will test the anti-cancer activity of radioiodide at the dose selected in Phase I portion.

You are being invited to take part in the Phase I portion of the study.

The experimental therapy used in this trial is a radioactive form of a chemical element called iodide ^{131}I-. This treatment is investigational because iodide ^{131}I-is not approved by the US Food and Drug Administration (FDA) to treat metastatic breast cancer and its activity in breast cancer is unknown. Iodide ^{131}I- is taken up mainly by the thyroid gland through a molecule called sodium/iodide symporter (NIS) which is also present in some breast cancer cells which provides

the rationale for this study. Iodide ^{131}I- is approved by the FDA to treat overactive thyroidits (inflammation of the thyroid gland) and thyroid cancers that take up iodine.

There is no certainty that Iodide ^{131}I- will benefit you and alternative standard of care therapies may be available for you to treat your cancer instead of participating in the trial.

Every possible measure will be taken to prevent or lessen toxicity on this trial but there is no certainty that these measures will be effective. There remains the risk of injury that may be severe, life-threatening or even fatal.

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

Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign and date where indicated on this form.

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

The research study is being funded by the Yale Cancer Center. The Yale Cancer Center is providing research support and study drug for this research study. Dr. Lajos Pusztai is the principal investigator of this study at Yale Cancer Center.

Purpose

The purpose of this Phase I study is to test 4 increasing doses of ^{131}I- radioiodide (30, 60, 120, and 200 mCurie/mCi) to determine which doses are safe in metastatic breast cancer. Treatment will only be given once to each patient. The effect of the treatment on your cancer is also assessed.

The researchers will start with the 60 mCi dose, which is the lowest dose where the drug still may work in thyroid cancer. If severe side effects are encountered in the first 3 patients, the next 3 patients will be treated with a lower dose of 30 mCi. If the first 3 patients have no side effects with the 60 mCi dose that would limit increasing the dose, the next 3 patients will receive 120 mCi. If these patients also have no side effects that limits increasing the dose, the next 3 patients

will receive 200 mCi. The goal of this stepwise increase in the dose is to find the highest tolerable dose that subsequently will be tested in a larger number of patients in the Phase II part of the study.

It is expected that a maximum of 24 patients will be enrolled in the Phase I portion of this study at Yale Cancer Center.

Study Procedures

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

Screening Period

If you agree to participate in this study you will need to take a thyroid hormone drug called Cytomel™ (liothyronine or T3) (*) 25 micrograms twice daily as a pill for 10-15 days and also adhere to a low iodine diet for a minimum of 5-7 days before taking pills of iodide ^{124}I- (6 mCi dose). Two days after taking the iodide ^{124}I- you will have a PET-CT (*) scan to find out in which organs we can detect iodide ^{124}I-. Iodide ^{124}I- is another form of a radioactive iodine, which produces much less radiation than the therapeutic iodide ^{131}I- (*) and is used to find organs through the PET-CT scan that take up iodide and to measure how much iodide is taken up by the different organs, including your cancer. ^{124}I- is approved by the FDA for this purpose.

The drug Cytomel™ is given for 10-15 days before taking the iodide ^{124}I- to reduce iodide uptake into your normal thyroid gland because radioiodine can damage your thyroid gland. The dose of Cytomel may be changed during this time period depending on the thyroid hormone levels in your blood that will be checked. If the PET-CT scan indicates that your cancer is taking up sufficient amounts of iodide, which will be determined by a physician who is an expert in using radioiodine to treat thyroid cancers, you will be eligible to receive treatment a few days after the scan with ^{131}I- that produces higher levels of radiation. Those who receive treatment with ^{131}I-, will also need to continue with Cytomel™ daily for until 7 days after the administration of the ^{131}I- treatment. Patients whose PET-CT shows no or very little uptake of iodide in the cancer, will not receive treatment with ^{131}I- and will only take Cytomel™ for until 3 days after the PET-CT scan.

A low iodine diet is necessary for 5-7 days before taking the ^{124}I- imaging marker in order to deplete your body of non-radioactive iodide that could prevent cells, including your cancer, from

taking up ^{124}I-. If you are eligible for therapy with ^{131}I, this low iodine diet will need to continue for until 24 hours after administration of ^{131}I-. The following are food items are rich in iodine and should be avoided during this period:

Iodized salt, milk, yogurt, cheese, ice cream, egg yolk, fish and crabs, liver, turkey meet, seaweed, milk chocolate, iodide containing vitamins, soy proteins

Patients must also discontinue iodide-containing medications:

Type of medication	Recommended time of withdrawal
Thionamide medications (e.g., propylthiouracil, methimazole carbimazole)	3 days
Multivitamins containing iodide	7–10 days
Kelp, agar, carrageenan, Lugol solution	2–3 week, depending on iodide content
Saturated solution of potassium iodide	2–3 week
Topical iodine (e.g., surgical skin preparation)	2–3 week
Intravenous radiographic contrast agents	4 week
Amiodarone	3–6 months

You will also need to undergo a series of additional laboratory tests to determine if you are eligible to participate in this study research study. The following tests or procedures will be performed during the visit(s) and must be performed within 4 weeks prior to receiving the study drug (^{131}I-):

- Complete physical examination including measurements of height, weight, and vital signs
- Review of medical history
- Blood samples for complete blood count including differential and comprehensive metabolic profile
- Blood samples for tumor markers - blood samples will be collected to analyze certain markers present in your tumor cells that are associated with your type of breast cancer and to study how different types of cells respond to the study drug.

- Blood samples for thyroid function tests which will include TSH (thyroid stimulating hormone) and free-T4 and T3 thyroid hormone levels (*).
- If you are a woman and you are able to have children, you must have a serum or urine pregnancy within 6 days or less before the iodine scan and/or administration of the radioiodide
- You will have a fluorodeoxyglucose (FDG) PET/CT scan without contrast to compare the results with the iodine PET/CT scan and to obtain baseline measurements of the cancer.
- If you have cancer in your bones, then you may need to undergo either magnetic resonance imaging (MRI) or an x-ray of the affected bones
- You may have a MRI of the brain if you have had cancer in your brain or if your study doctor thinks it is necessary

If you complete all of the screening procedures and your doctor determines that you are eligible, you will move on to the Treatment Period which is described on the next page.

If the iodine PET/CT scan shows low iodide uptake you are not eligible to receive therapy with the study drug, but the following safety assessments will be performed every 2 weeks for the first 4 weeks after the ^{124}I-PET-CT:

- Review of medical history including medications you have taken or are currently taking and any adverse events you have experienced
- Physical examination including measurements of weight and vital signs
- Complete blood count and comprehensive metabolic profile
- Blood samples for thyroid function tests

Treatment Period

If your study doctor has determined that you are eligible to participate in the treatment part of the study, the following procedures will take place:

If your study doctor determines that you have tumor tissue that may be obtained with a minimum of risk and discomfort to you, he or she will ask you if a small sample of your tumor tissue may be obtained by biopsy sample collection before you receive the ^{131}I- radioiodide (*). The tissue sample will be used to assess NIS expression. As mentioned on the first page of this form, NIS is a molecule called sodium/iodide symporter (NIS) that takes up ^{131}I- and is present in some breast cancer cells. Your study doctor will explain the details of the procedure to you. This is an optional procedure and you will be asked to mark your choice at the end of this form.

Within one week of having the ^{124}I imaging, you will be given ^{131}I- radioiodide orally in the form of a capsule. This is a one-time, outpatient therapy. Your study doctor will tell you what your dose of radioiodide will be. Because the study drug is radioactive, you will need to come to a clinic that is specialized in radiation safety to receive your dose of radioiodide. You should not eat or drink anything for 2 hours before you receive your dose of ^{131}I- radioiodide.

Five to seven days after you have taken the ^{131}I- radioiodide capsules, an imaging test will be performed using a device called gamma-camera, to examine the distribution of the drug in your body.

The following assessments will be performed after you receive your dose of radioiodide, every week for the first 4 weeks (+/- 2 days):

- Review of medications you have taken or are currently taking and any adverse events you have experienced
- Physical examination including measurements of weight and vital signs
- Blood samples for complete blood count including differential and platelets
- Blood samples for thyroid function tests (*)

The following assessments will be performed when you receive your dose of radioiodide and then every 4 weeks (+/-4 days) after that until disease progression:

- PTT, PT, and INR
- Complete metabolic profile
- Blood samples for tumor markers (this will continue to be collected only if your initial blood test showed tumor markers)

The following evaluations will be performed every 8 weeks (+/- 4 days) after you receive your dose of ^{131}I until disease progression:

- [18F]FDG PET/CT scan without contrast to assess tumor response.
- Bone metastasis will be assessed by repeat MRI or plain x-ray in patients who had bone metastasis at baseline or if clinical suspicion for new bone metastasis.
- MRI of the brain if known brain metastasis at baseline

Some procedures may be done more frequently if your doctor thinks it is necessary.

End of Treatment

If your cancer gets worse (progresses), you will need to return to the clinic for an end of study evaluation. The following procedures will be performed:

- Review of medical history including medications you have taken or are currently taking and any adverse events you have experienced
- Physical examination including measurement of weight and vital signs
- Complete blood count, including differential and platelets, and complete metabolic panel
- Blood samples for thyroid function tests

Follow-up Period

Once you have completed the treatment period, you will be followed by your study doctor until your cancer gets worse and any adverse events you experienced during the treatment period have resolved.

Patients will also have yearly blood samples for TSH measurement after progression until death or hospice transfer, to find out if long term damage to the thyroid gland develops or not.

Follow-up visits to assess your health status will also be scheduled 20, 36 and 52 weeks after receiving treatment.

Potential Risks, Side Effects, Discomforts and Inconveniences

Risks associated with radioiodide:

While in this study, you may have side effects. Anticipated side effects are listed here. In addition to the risks listed below, there may be risks that are currently unknown. If significant new risks develop during the course of study that might affect your willingness to participate, information will be reported to you as soon as possible. Possible side effects that you may experience during this study will be fully explained to you by the study staff. Please ask as many questions as you want so that you can understand the possible side effects of your specific treatment before you decide whether you want to be in this study. Please ask the study doctor or the study staff to explain any information or words that are not clear to you.

Radioiodide ^{124}I- used during the imaging screening step of the study usually does not cause side effects because of the low radiation dose. However, potential rare side effects include those described below as side effect of the therapeutic radioidide.

Radioiodide ^{131}I- as therapy is frequently given to people with thyroid cancer at doses of 50-200 mCi, and also to patients with thyroid inflammation that causes hyperthyroidism (which is a condition when the thyroid gland is releasing too much thyroid hormones) at doses of 4-10 mCi.

Common side effects that have been reported with doses of radiodiodide used in the treatment of thyroid cancer include:

- Bone marrow depression, which is a decrease in production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes)
- Anemia (a deficiency in red blood cells or hemoglobin in the blood)
- Leucopenia (a reduction in the number of white cells in the blood)
- Thrombocytopenia, which is a deficiency of platelets in the blood and may cause bleeding into the tissues, bruising, and slow blood clotting after injury
- Blood dyscrasia (a diseased state of the blood)

Rare side effects that have been reported with doses of radiodiodide used in the treatment of thyroid cancer include:

- Leukemia, which is a malignant disease in which the bone marrow and other blood-forming organs produce increased numbers of immature or abnormal leukocytes
- Solid cancers, which are defined as abnormal cellular growths in "solid" organs such as the breast or prostate, as opposed to leukemia, a cancer affecting the blood, which is liquid
- Lacrimal gland dysfunction (a malfunction in the glands that produce tears)
    - Symptoms include dry eyes, swollen eyelids, or excessive watering of the eyes
- Salivary gland dysfunction (a malfunction in the glands that produce saliva)
- Cerebral edema (swelling in the brain caused by the presence of excessive fluid)
- Radiation pneumonitis (inflammation of the lungs caused by exposure to radiation)
- Pulmonary fibrosis (damage or scarring on the lung or lungs)
- Hypothyroidism (an underactive thyroid) which may be permanent and require thyroid hormone replacement for the rest of your life.
- Symptoms of radiation sickness include nausea, hair loss, diarrhea, and bleeding.

Rare side effects that have been reported with doses of radiodiodide used in the treatment of thyroiditis include:

- Sialadenitis (inflammation of the gland that produces saliva)
- Chest pain
- Tachycardia (increased heart rate)
- Iododerma (a skin lesion caused by an iodine sensitivity)
- Itching skin
- Rash
- Hives
- Hypothyroidism (an underactive thyroid) which may be permanent and require thyroid hormone replacement for the rest of your life
- Hyperthyroidism (an overactive thyroid) that usually transient.
- Thyrotoxic crisis, which is a rare but severe and potentially life-threatening complication of hyperthyroidism
    - Symptoms include high fever (often above 40°C/104°F), fast and often irregular heartbeat, vomiting, diarrhea and agitation
- Hypoparathyroidism, which is a rare condition in which the thyroid doesn't make enough of a hormone that regulates the amount of calcium and phosphorous in the body
- Local swelling

The following rare side effects have also been reported, typically around the third day after administration of radioiodide:

- Tenderness
- Pain on swallowing
- Sore throat

- Cough

The following rare but potentially serious adverse reactions have occurred in people who have received radioiodide:

- Radiation-induced thyroiditis (inflammation of the thyroid caused by exposure to radiation). Radiation thyroiditis is a rare complication of ^{131}I- therapy (1-5% of cases), however, the risk of radiation thyroiditis may be higher in patients who have intact thyroid gland.
- Thyroid enlargement – some of the drugs that are commonly given to manage the side effects of radioiodide can cause your thyroid to overproduce some hormones and become enlarged
- Radiation-induced toxicities (including death) – radioiodide may cause an increased risk of neoplasia, which is a new, uncontrolled growth of cells and can be either cancerous or noncancerous
- Hypersensitivity Reactions – the study drug contains sodium bisulfite, a sulfite that may cause allergic-type reactions that can be life-threatening. Sulfite sensitivity is seen more frequently in people who have asthma.

<u>Radiation Safety after therapy with ^{131}I iodide:</u>

In general, the administration of radioactive drugs involves a potential risk for people other than the subject due to possible contamination due to spilling of the subject's bodily fluids, such as urine or feces. Any radioiodide in your stool or urine does not present a significant risk to others if standard hygiene measures are followed.

*During first 24 hours after ^{131}I– treatment***:** Prolonged use of public transportation is discouraged for the first 24 hours after ^{131}I- therapy.

*During first 7 days after ^{131}I treatment (SNMMI guidelines)***:**

- Patients should sleep alone for the first 7 days after ^{131}I- treatment.
- During this period, patients should avoid kissing or sexual intercourse.
- Avoid contact with children and pregnant women because the thyroid glands of children and the unborn are more sensitive to the effects of radiation than those of adults. Pregnant women and children may have about 10 min of zero distance per day from the patient but otherwise should maintain a distance of about 0.9–1.8 m (3–6 ft). Infants and small children requiring feeding, changes of clothing, and similar care from the treated parent will require another caregiver for up to a week.
- There is no hazard to any member of the family arising from sites where the patient sits, what the patient has touched, or what the patient cooks.
- Discontinue breast-feeding and pumping at least four weeks before administration of sodium iodide ^{131}I-. Radioiodine passes into the breast milk and may cause unwanted effects in the nursing baby, such as an underactive thyroid. The patient

may not resume breastfeeding for that child. Nursing may resume with the birth of another child.

- Both female and male patients with reproductive potential must use two effective methods of contraception to avoid pregnancy for at least 6 months after ^{131}I-administration.
- For male patients there is a possibility of transient infertility. The radiation dose to the testes can be reduced by frequent voiding. Sperm storage before high-dose ^{131}I therapy may be considered, since the post therapy sperm count may not return to normal when higher doses of ^{131}I are administered. Impairment of female fertility by ^{131}I therapy has not been as well described.
- Patients must wash their hands thoroughly with soap and plenty of water for at least 20 seconds each time she/he goes to the toilet. Please flush the toilet 2 times after each use.
- Rinse the bathroom sink and tub thoroughly after she uses them. Men should urinate sitting down to avoid contamination in the toilet area. Clean bathroom habits will reduce the chances of others becoming contaminated by the radioiodine in a patient's saliva and sweat.
- Patients should drink plenty of liquids such as water or juices. This will increase urine production which helps the radioiodine to leave the body more rapidly, thus lowering the amount of radioiodine remaining in the body. Good hydration means drinking about 2,500–3,000 mL of any liquid except milk for an average-sized adult patient with normal kidney function.
- In addition to good hydration, it is important to stimulate the flow of saliva by chewing sugar-free candy or gum in order to reduce radiation exposure to the salivary glands.
- Void your bladder frequently (about hourly) for several days to a week to reduce radiation exposure to the bladder and salivary glands.
- Make sure you have at least one bowel movement a day to reduce colon exposure. Laxatives (but not stool softeners which do not stimulate the bowel) may be necessary in constipated patients
- Disposable plates and utensils are not only unnecessary but, if used, can trigger sensitive waste facility alarms; dishes and utensils should not be shared before washing. This will reduce the chance of contaminating other family members with the radioiodine in your saliva.
- Must use separate towels and washcloths, however, it is unnecessary to wash the patient's laundry separately.
- Patients must be provided with a written document stating they have been given a radioactive substance for documentation of the source of radiation in case it is detected by monitoring devices during travel.

During First 6-12 months post ^{131}I– treatment:
Both men and women wait for 6–12 months after ^{131}I therapy before trying to conceive a child.

Other Risks

There no known risks involved with following a low iodine diet for a short period of time (18-28 days).

Cytomel™ (Liothyronine, T3):
Liothyronin is a synthetic form of the naturally occurring thyroid hormone, L-triiodothyronine, also called as T3. This drug is approved by the FDA as hormone replacement therapy in patients with hypothyroidism and also as a diagnostic agent to suppress the production ofthyroid-stimulating hormone and allow diagnostic imaging of the thyroid gland with radioiodide. Side effects of this drug represent symptoms of too much thyroid hormones including headache, irritability, nervousness, sweating, rapid and/or irregular heartbeats, diarrhea, menstrual irregularities. Angina pectoris or congestive heart failure may be induced or aggravated.

Tumor Biopsy:
As with any procedure, there are risks and discomforts. You may feel some amount of pain or discomfort during a biopsy, including slight, stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness, inflammation, bleeding, swelling, and/or infection at the biopsy site. With a tumor biopsy, there is a rare possibility of tumor cells spreading into the nearby area. If a general anesthetic is used, you will not feel pain during the procedure because you will be asleep. Your physician will explain the details of the procedure and the risks to you, depending on how the biopsy will be obtained.

Blood Collection:
The risks of taking blood may include pain, redness, swelling and/or bruising where the needle enters your body, light-headedness and fainting. On rare occasions, local blood clot formation or infection with redness and irritation of the vein has occurred. The blood pressure cuff may cause discomfort or bruising to the upper arm. Approximately 20 mL of blood will be taken from you every week during the first 4 week of treatment and every 4 weeks thereafter.

FDG-PET:
FDG-PET scans require an injection of a small amount of radioactive tracer (18 fluorodeoxyglucose) that is considered safe, and these tests are routinely given to many cancer patients. There may be some discomfort similar to a pinprick for the IV delivery of the radioactive tracer dye used in these scans. There may be pain and a small risk of bruising and/or infection at the place where the needle is inserted. Also, there might be some anxiety and claustrophobia (a fear of being in narrow or enclosed spaces) associated with the scanner.

Since the radioactivity is very short lived, your radiation exposure is expected to be low. This radiation exposure is not expected to affect the normal processes of the body.

MRI:
There are no known risks or side effects with having an MRI. If a contrast material is used, your study doctor will tell you about possible side effects or allergic reaction.

Brain MRI scan:
You may not have an MRI done if you have metal in your body, for example, some hip replacements, hearing aids, pacemakers, bullets, or jewelry that cannot be removed. You should inform the technologist or physician if you have any metal in your body. During the MRI exam, you may feel some heat and hear tapping noises but have no reason to worry. Some people may have a 'closed in' feeling while inside the machine. The injection may make you sick to your stomach or have pain, warmth, swelling, bruising, a small blood clot or infection at the injection site. Rarely, you may get a rash or other signs of allergy from the injection or get a rare disease where some of your body parts get scarred. If you have a history of kidney problems you must inform the technologist or physician as you may not be able to receive an injection during the MRI exam. Please talk to your physician if you have any concerns or questions.

Risks associated with gadolinium contrast:
You may have a small IV catheter placed before the MRI scan so that gadolinium contrast can be injected into a vein as this may help to better determine if your cancer has spread. With gadolinium contrast severe reactions are rare. The FDA approves the contrast agent Gadolinium for use with human participants. You need to know that there are certain risks associated with the use of that contrast. Some healthy subjects (fewer than 3%) may experience mild nausea, headache or dizziness after the injection. These side effects usually resolve without need for treatment. There is also a risk of allergic reaction (less than 1%). An allergic reaction can cause hives and itching or difficulty breathing. In individuals with kidney dysfunction, the gadolinium can cause a serious condition called nephrogenic systemic fibrosis. Because of this, prior to your MRI scan you will have to undergo blood work to make sure that your kidney function is normal.

Detailed information on the contrast agent Gadolinium can be provided to you at your request. You should inform your study doctor: (1) if you are pregnant or breast feeding, (2) if you have a history of allergic reactions to MRI or CT contrast agents, (3) if you have a history of kidney disease, seizure, asthma, or allergic respiratory disorders, and (4) if you have anemia or disease that affects red blood cells.

Bone scan:
A radioactive substance is injected into a vein in your arm. There is a slight risk of damage to cells or tissue from being exposed to any radiation, including the radiation released by the substance in this test. Side effects at the injection site may include pain, redness, swelling, and/or bruising where the needle enters the body. Some people can have allergic reactions to the substance put in their veins for this test. The allergic reactions can cause itching or rash. More serious allergic reactions can cause difficulty breathing, dangerously low blood pressure, or kidney damage.

Reproductive Risks:
Radioiodide being passed through the placenta can cause severe and possibly irreversible hypothyroidism (underactive thyroid) in a fetus. Radioiodide can also be transferred to an infant through breast milk. If you are breastfeeding or breast-pumping, you should stop at least four weeks before you receive radioiodide. Because of this, you will not be eligible to participate in the study if you are pregnant, trying to become pregnant, or breastfeeding/breast-pumping. To avoid any risks, the study doctor will take the following precautions:

- If you are a woman of child-bearing potential, you must undergo a serum or urine pregnancy test and have a negative result within 72 hours or less before having the iodine PET/CT scan and/or before receiving your dose of radioiodide.
- If you are a sexually active woman or man of reproductive potential, you and/or your partner will be required to use two effective methods of birth control during the study and for at least six months after your dose of radioiodide.
- If you or your partner becomes pregnant during the study or is planning to breastfeed/breast-pump, please inform your study doctor immediately. Radioiodide may cause congenital hypothyroidism (loss of function of the thyroid gland) and chromosomal abnormalities (missing, extra, or irregular portions of DNA) in newborns.

There is a potential that radioiodide can cause infertility. There have been reports of impaired testicular function in men and ovarian failure in women who have received radioiodide. If you are a male of reproductive potential, you can talk to your doctor about the possibility of sperm banking before receiving radioiodide.

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

For more information about risks and side effects, ask the researcher or contact their office at (203) 737-8309.

Benefits

If you agree to take part in this research study, we cannot guarantee that you will receive any benefits. We hope the information learned from this research study may benefit other patients with metastatic breast cancer in the future.

Economic Considerations

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

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

Taking part in this research study may lead to added costs for you or your insurance provider. You are encouraged to speak with your insurance provider prior to entering the research study to find out your individual coverage. If you have difficulty determining your individual insurance coverage, you may call Dr. Lajos Pusztai's office for assistance at (203) 737-8309.

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

Treatment Alternatives

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

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

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

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

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

The protected health information that will be collected in this study includes demographics, medical history, physical examinations, routine lab tests, review of adverse events and medications you take (past and present), vital signs, MRI scans, FDG-PET scans, pregnancy tests, blood or tissue samples for research purposes, survival follow-up information and records about any study drug(s) that you received.

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

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

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

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

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

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee or Institutional Review Board that reviews, approves, and monitors research

on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential

- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The study doctor, Dr. Lajos Pusztai, and the Yale study team
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The manufacturer of the study drug, Mallinckrodt Pharmaceuticals, and/ or their representatives
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

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

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

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

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, you will not be allowed to look at or copy your study related information until after the research is completed.

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

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

In Case of Injury

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

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

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

Withdrawing From the Study:

If you decide to participate in this research study, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. They will make sure that proper procedures are followed and a final visit is made for your safety. This will cancel any future research study appointments. You may request that your sample(s) be destroyed by contacting your study site. As long as it is possible to identify your samples (i.e., your samples have not been anonymized or the study site has not destroyed the first key), then your sample will be destroyed. However, data obtained from your samples prior to receiving your request for destruction will not be deleted. If you request destruction of your sample(s), you will not lose any benefits, medical treatment or legal rights to which you are otherwise entitled.

The researchers may withdraw you from participating in the research if necessary. The study doctor can withdraw you from receiving treatment on this study because of the following reasons:

- If continued participation in the study is not beneficial to you in your doctor's opinion
- If you develop an illness that makes receiving radioiodide too risky
- When your breast cancer progresses despite radioiodide therapy
- If you need to take other medications that are not allowed

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

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

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

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

Questions

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

Optional Fresh Tumor Biopsy (before $^{131}I^-$ administration)

Please indicate your choice below by checking yes or no:

_____ Yes, I willingly consent to undergo a fresh tissue biopsy of my tumor and allow the sample to be used for assessment of NIS expression as described earlier in this form

_____ No, I do not agree to undergo a fresh tissue biopsy of my tumor

Authorization and Permission

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

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

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

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

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

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Lajos, Pusztai, at (203) 737-8309. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.