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CONSENT FORM FOR A RESEARCH STUDY

Title: A Phase Ib Study to Assess the Safety, Tolerability and Immunologic Activity of Preoperative IRX-2 In Early Stage Breast Cancer (PH&S IRB #16-126B)

Principal Investigator: David Page, MD

Sponsor: Providence Cancer Center

INTRODUCTION AND PURPOSE

You are being asked to take part in this research study because you have early stage breast cancer (ESBC) and are planning to have surgery to remove the tumor, or planning to have chemotherapy prior to surgery (for patients with a certain type of breast cancer called 'triple-negative' breast cancer).

This consent form will explain this study to you, and what you need to do if you take part. Make sure you understand what is written, and ask as many questions as needed before you decide whether to take part. After this study has been explained to you, and if you choose to take part, you will be asked to sign this consent form.

Standard care for early stage breast cancer is surgery, which may be followed by radiation treatment and/or hormone treatment. Sometimes, chemotherapy is also used to treat breast cancer, and may be given either before surgery or after surgery.

Patients who decide to join this study will receive a treatment regimen called IRX-2.

For patients with early stage breast cancer, the IRX-2 regimen will be given before surgery.

For patients with triple-negative breast cancer, the IRX-2 regimen will be given prior to the recommended chemotherapy treatment, which is followed by surgery.

The IRX-2 regimen is an investigational (not approved by the Food and Drug Administration - FDA) treatment. IRX-2 is a mixture of proteins made by human cells stimulated in a laboratory to make these substances (proteins) that can "turn on" the immune system. IRX-2 has been shown to shrink cancer tumors in other types of cancer, and may be helpful in treating breast cancer. Following the IRX-2 treatment, all patients will receive the standard care treatment recommended by their doctor.

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This is a phase I study. A phase I study tests an investigational medication in a small number of people to evaluate safety, find a safe dose, and identify side effects. Testing the effectiveness is not the main goal of this study. You may not benefit personally from the study regimen, but this study may lead to further research in patients with more advanced breast cancer who may be more likely to benefit from the study regimen.

The study regimen consists of an investigational treatment called IRX-2, given along with several other FDA-approved medications (cyclophosphamide, indomethacin, omeprazole, and multivitamins with zinc):

- IRX-2: The immune system is sometimes able to detect and kill cancer cells. One reason breast cancers arise may be that the immune system is defective and unable to kill the cancer. IRX-2 is an injectable drug made from human immune cells, and is composed of substances (proteins) that are thought to stimulate the immune system to fight cancer. IRX-2 may increase the immune system's ability to fight breast cancer.
- Cyclophosphamide is an FDA-approved drug that is used to treat many kinds of cancer, including breast cancer. In this study, however, it is being used to turn off cells that may prevent the immune system from killing cancer. Its use in this study is investigational, and the dose used is lower than the dose that would be used to treat breast cancer.
- Indomethacin is an FDA-approved drug that has been used for many years to treat pain or inflammation. In this study, it is also being used to "turn off" inflammation that may prevent the immune system from killing the cancer. Its use in this study is investigational.
- Omeprazole is an FDA-approved drug used to protect the stomach from irritation that can be caused by indomethacin.
- Many patients with cancer have low levels of zinc. Researchers have found that low levels of zinc can weaken your immune response, so multivitamins with zinc will be given.

The main purpose of this study is to find out the effects, good and/or bad, the IRX-2 regimen has on patients with breast cancer. The study will also identify any side effects of the study regimen. Everyone who joins this study will receive the IRX-2 regimen. This study will also collect blood and tumor tissue for research purposes, including genetic testing.

About 39 people will take part in this study.

STUDY PROCEDURES

This study occurs in three periods, a screening period, a treatment period, and a follow-up period. During the screening period you will have the following tests and procedures to see if you are eligible to receive the study treatment. These tests will occur within 3 weeks of starting the study treatment:

- Medical history review
- Physical exam and evaluation of your ability to complete day-to-day activities
- Blood test to evaluate your organ function (liver and kidney), to count the different types of cells in your blood, and the clotting ability of your blood
- Pregnancy test if you are able to become pregnant
- Tumor tissue will be collected, either from a previous biopsy or a new biopsy

TREATMENT PERIOD

If the screening tests show you can be in this study, and you still choose to take part you can begin the study treatment. During the treatment period, you should avoid the use of alcohol,

aspirin, and ibuprofen or other anti-inflammatory medications, unless reviewed and deemed safe by the research team.

On Day 1 of treatment you will receive cyclophosphamide through a vein in your arm (IV) over 30 to 60 minutes. Also, you will take Indomethacin (3 times each day), a multivitamin with 15-30 mg of zinc (once each day), and Omeprazole (once each day) by mouth for 21 days. IRX-2 will be given on ten consecutive weekdays between Days 4 and 19. On days when IRX-2 is given, you will receive two injections under the skin of the breast that contains the tumor, near the nipple. These injections are similar to receiving a vaccine under the skin. You will need to come to the clinic each day to receive your IRX-2 injections. The table below shows the study treatment regimen.

Days of administration	**Drug**	**Route**
1	Cyclophosphamide	IV
Any 10 consecutive weekdays between days 4-19	IRX-2	Two injections
1-21	Indomethacin	By mouth
1-21	Multivitamin with 15-30 mg of zinc/tablet	By mouth
1-21	Omeprazole	By mouth

On Day 1 of the study treatment, you will be asked about any signs or symptoms from your breast cancer, have blood drawn to evaluate your organ function (liver and kidney) and to count the different types of cells in your blood. You will also have blood drawn for research tests before you receive cyclophosphamide to help see how your immune system reacts to the study treatment.

During the treatment period, you will have blood drawn on the day you start IRX-2 injections and after about 5 and 10 days of IRX-2 injections. You will also have blood drawn on the day of surgery or your post-treatment biopsy, as well as during a follow-up visit approximately 30 days later. The blood will be used for routine lab tests and for research tests to see how your immune system is reacting to the study regimen. About 3 tablespoons of blood for research will be drawn at each visit. At each of these visits you will be asked about any signs or symptoms of your breast cancer, any side effects you may be experiencing, and any medications you are taking.

Either breast surgery or a repeat biopsy will be scheduled to occur within 12 days of the last IRX-2 injection, ideally 2-5 days after the last IRX-2 injection. You will stop indomethacin at least two days prior, even if the planned 21 day course has not been completed. Before surgery or biopsy, you will have a physical exam, you will be asked about any signs or symptoms of your breast cancer, any side effects you may be experiencing and any medications you are taking. A sample of tumor tissue removed during surgery will be used for research.

Early Stage Breast Cancer
About 30 days after surgery, you will return for a follow-up. At this visit you will have blood drawn, a physical exam, you will be asked about any signs or symptoms of your breast cancer, any side effects you may be experiencing and any medications you are taking.

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Triple Negative Breast Cancer
After the IRX-2 regimen, you will continue to have routine visits with your doctor while receiving the chemotherapy you will get before surgery

Following the study, the research team will continue to follow you, either during routine clinical appointments or by other methods such as reviewing your medical records or by telephone. This follow-up will help to determine whether IRX-2 influences long-term risk of breast cancer.

Tissue Research
Blood samples and the tissue removed during the biopsies and your breast surgery will be used for research, including genetic research. This research is being done to find out how many and what types of immune cells are in your tumor and for future research questions. These samples will not be labeled with your name, but a code number. Samples will be stored indefinitely in a secure location at the Earle A. Chiles Research Institute at Providence Portland Medical Center (4805 NE Glisan St., Portland, Oregon, 97213).

If you choose to withdraw your consent, contact your study doctor. Any specimens that remain will no longer be used for research and will be destroyed. However, any testing and results obtained before you withdrew your consent will still be used as part of this study.

These samples will be used only for research, and will not affect your care or treatment. Neither you nor your family will be told the results of these tests. The results will not be included in your medical record.

POSSIBLE RISKS OF IRX-2
There may be certain risks to you if you take part in this study. Side effects currently unknown may occur, including possible interaction with other medications you may be taking. Most of the side effects seen in patients treated with IRX-2 were described as mild or moderate in severity. In most cases, side effects go away after the study treatment is stopped; however, some may be serious, permanent, or even cause death. If you have any side effects, you should report them to your study doctor or the research staff.

The risks below occurred in more than 10 patients out of 100

- Lowered number of white blood cells which may increase your risk of infection
- Lowered number of red blood cells (anemia) that may lead to tiredness and/or shortness of breath
- Increased number of white blood cells (neutrophilia) which may cause abnormal blood test results and may indicate infection, inflammation, or drug reaction, but is unlikely to cause any symptoms
- Difficulty swallowing
- Loss of appetite (anorexia)
- Shortness of breath
- Abdominal pain
- Headache
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Injection site reaction – you may experience pain, bruising, bleeding, or swelling where the needle enters your breast; infection or fainting happen rarely.

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- Runny nose
- Nausea
- Fever
- Diarrhea
- Weakness, feeling weak (asthenia)
- Lowered level of albumin (hypoalbuminemia), a normal protein in the blood which may indicate nutritional deficiencies but is unlikely to cause symptoms, but could cause fluid build-up (called edema) that may cause swelling of your body
- Dehydration – not enough fluid in the body that may cause thirst, or dry mouth, dry skin or mucus membranes, or darker urine. Severe dehydration may cause low blood pressure, dizziness, fast heart rate, fever, or confusion.
- Low blood pressure (hypotension) which may cause you to feel faint or dizzy
- Pain (most commonly near injection site)

POSSIBLE RISKS OF CYCLOPHOSPHAMIDE

The below list describes the risks associated with cyclophosphamide when given at the FDA-approved dose and schedule to treat breast cancer. As part of this study, you will receive only a single, low dose of cyclophosphamide. Therefore, the likelihood of experiencing these side effects is anticipated to be lower than stated in the below list.

Frequent (at least 20 people out of 100)

- Nausea and vomiting
- Decreases in white blood cells, which could lead to infection
- Decreases in red blood cells causing fatigue and shortness of breath, which could require a transfusion.
- Irritation of the bladder. This could cause pain with urination or blood in the urine.
- Fatigue
- Hair thinning
- Loss of appetite
- Diarrhea
- Stomach pain
- Mouth sores

Less frequent (between 5 and 19 people out of 100)

- Discomfort or bruising where the needle is inserted to give the infusion
- Shortness of breath
- Cough
- Chest tightness

POSSIBLE RISKS OF INDOMETHACIN

Common (10 or more patients out of 100)

- Increase in liver enzymes which is not likely to cause symptoms
- Headache
- Nausea
- Dizziness

Less Common (2 – 9 patients out of 100)

- Abdominal pain

- Constipation - difficult bowel movements
- Diarrhea
- Indigestion
- Lethargy or sleepiness
- Dizziness
- Ringing in the ears

Rare (less than 1 patient out of 100)

- Bronchospasm – narrowing of the airways which may cause chest pain or tightness, difficulty breathing or wheezing.
- Heart failure (the pumping action of the heart weakens) which may cause tiredness, swelling of the feet and legs, trouble breathing, chest pain, or changes in heartbeat
- Bleeding or damage of the gastrointestinal tract which may cause bloody stools, blood in vomit, or vomit which looks like coffee grounds. **The use of alcohol may increase your risk of stomach bleeding and should be avoided**.
- Kidney damage which may have no symptoms, but if severe could require dialysis
- Hearing loss
- Disease of the retina which may cause blurred vision
- Allergic reaction to medication
- Abnormal liver function tests which may indicate liver damage and may cause jaundice (yellowing of the skin), fatigue, weakness, shortness of breath, excessive bruising or bleeding, and leg swelling, or liver failure
- Skin problems such as Stevens-Johnson syndrome which may cause skin rash, redness, blisters, facial or tongue swelling, or Toxic epidermal necrolysis - a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling that of a severe burn.

POSSIBLE RISKS OF OMEPRAZOLE AND MULTIVITAMINS WITH ZINC

Multivitamins with zinc may cause stomach irritation. Omeprazole is unlikely to cause side effects. All possible side effects from the combination of IRX-2, cyclophosphamide, indomethacin and omeprazole are unknown at this time. Your study doctor will discuss with you the possible risks involved with these other study drugs that you are required to take in this study.

Please tell your study doctor or nurse about all the prescription drugs, herbal products, over-the-counter drugs, vitamins and natural remedies that you are taking before you start the study. Your study doctor may ask you to stop taking some of these products while you are taking part in this study.

POSSIBLE RISKS OF BIOPSY

Some participants, including patients with triple negative breast cancer who are to receive chemotherapy before surgery, will undergo a biopsy for research. Although a breast biopsy is relatively simple and its risks are low, every surgical procedure carries a risk. Some possible side effects of a breast biopsy include:

- an altered appearance of your breast, depending on the size of the tissue removed
- bruising/bleeding in the breast
- swelling of the breast

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- soreness at the injection site
- an infection of the biopsy site

Most of these possible side effects are temporary. If they're persistent, they can be treatable. Be sure to follow your doctor's instructions for care after the biopsy. This will greatly reduce your chance of infection.

Complications from a biopsy are rare.

Genetic Testing

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Pregnancy/New Father Warning

If you are pregnant or breastfeeding, you cannot take part in this study. The risks of the study treatment to an unborn baby or nursing child are not known and may cause harm. You may be required to have a blood and/or urine pregnancy test to see if you are pregnant before you begin this study treatment.

If you are sexually active, you must take adequate precautions to avoid the possibility of becoming pregnant while in this study. You must discuss these precautions with your study doctor before agreeing to take part in this study.

If you become pregnant, or your partner becomes pregnant during this study, you should tell your study doctor immediately. If you become pregnant, you will no longer be given the study treatment. If you agree, your study doctor will collect information about the pregnancy, the outcome of the pregnancy and the health of your baby.

After you complete this study treatment, check with your study doctor to see when it might be safe to breastfeed or become pregnant. After you complete your study treatment, it is important that you continue to take adequate precautions to avoid the possibility of becoming pregnant or a new father for at least 1 year.

POSSIBLE BENEFITS

There are no guaranteed benefits to you for taking part in this study. This study treatment may even harm you. However, if effective, this study treatment may lower the chances of your cancer coming back.

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The information learned from this study will help researchers learn more about IRX-2 and early stage breast cancer, and may help future patients.

OTHER TREATMENTS

You may choose not to take part in this study. Other treatments available to you include:

- Standard treatment(s) with chemotherapy and/or radiation therapy
- Other research study treatments, if available
- No treatment
- Supportive care to manage your symptoms and help make you comfortable

Your study doctor will review these with you before you decide to take part in this study.

GENERAL INFORMATION

Your taking part in this study is voluntary. Your refusal to take part will not affect the health care benefits you have. If you decide to take part, you are free to stop at any time without any effect on your medical care, your relationship with your doctor(s) or Providence Health & Services.

While in this study, any important new information that may affect your wish to continue taking part will be given to you.

Your study doctor may remove you from this study at any time if he/she thinks it is medically necessary, you have a serious side effect, or you do not follow the study plan.

COSTS

You will not be paid to take part in this study.

You are responsible and must pay for the costs of your routine medical care and medications; however, these costs may be covered, at least in part, by most major insurance companies or Medicare.

IRX-2, cyclophosphamide, indomethacin, and the multivitamins will be provided at no cost to you. The study sponsor will pay for all study-related tests required for this study, such as the research testing of blood and tumor tissue. The study doctor and the research coordinator will be responsible for making sure these tests are billed to this study, and not you or your insurance company.

Providence Portland Medical Center is being provided funding from IRX Therapeutics, Inc. (the manufacturer of IRX-2) to conduct this study. This is to pay for tests and to conduct this study.

You will not benefit financially if this study results in new treatments.

LIABILITY

If you are injured as a result of taking part in this study, all of the necessary medical facilities are available for treatment, as is reasonably possible.

If you are injured during this study, the study will cover the costs to treat an injury that is a direct result of taking part in this study if your insurance or Medicare does not cover the services provided.

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You do not give up any of your legal rights by signing this consent form and taking part in this study.

PRIVACY

Your medical and study records are personal and private and only your study doctor, yourself and anyone you allow have the right to look at your records. It is important that the research staff, IRX Pharmaceuticals (the manufacturer of IRX-2), the FDA, the Center for Medicare and Medicaid Services (CMS), and the Providence Health & Services Institutional Review Board (IRB – a committee that reviewed this research to protect your rights) be able to look at your medical and study records. When you sign this consent form, you agree to allow this. If results of this study are reported in medical journals or at meetings, your identity will remain secret.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) gives you certain rights to protect the privacy of your medical information and records. Under HIPAA, you must give your permission before anyone uses or shares your medical information. This information is also called protected health information (PHI). Your rights, as well as the reasons for using your PHI, are described below.

Your study doctor(s), IRX Pharmaceuticals, and the research staff will need to use your PHI for this study. Your study doctor will record PHI about you on study forms. This includes your name, address, telephone number, date of birth, past medical records and the results of tests and procedures done during this study.

By signing this consent form, you agree to allow your study doctor and the research staff to use and share your PHI for the following reasons:

- Make decisions about your medical care
- Evaluate the results of this study
- Make conclusions about the study results
- Provide study results to other study doctors
- Re-evaluate study results in the future, as needed
- Include your study information with results from other similar studies
- Send study information to government health agencies (for example, to the FDA to request approval of the treatment used in this study); this may also include government agencies in other countries
- Report side effects to the FDA and other government agencies
- Send study information to representatives of the study sponsor
- Any other purposes as described in this consent form.

If you are not willing to allow your PHI to be shared, you will not be able to take part in this study.

The IRB and any regulatory agencies may review your medical records and make copies. The reasons this might happen is to make sure this study is being done properly, study information is being collected correctly, and for other purposes allowed by law.

Once your PHI is shared with others, it is no longer protected by HIPAA law. However, it will be kept as confidential as possible.

Your permission to use and share your PHI will not end unless you change your mind. You may cancel your permission at any time by sending a written notice to your study doctor. Your PHI for

this study will no longer be collected. In some circumstances, your study doctor will need to use or share your PHI that has already been collected to continue this research study.

If you cancel your permission, you will no longer be able to take part in this study. Your study doctor will still use any PHI they received before you cancel your permission.

If you have questions about your privacy rights, please call the Providence Health & Services HIPAA Privacy Officer at (503) 574-9123.

QUESTIONS:
Any questions you have about this research study or a research-related injury can be answered by:
Study Doctor: _____ at _____

Research Coordinator: _____ at _____

Any questions you have about your rights as a research subject will be answered by the Providence Health & Services Institutional Review Board at (503) 215-2046.

You are free to ask questions about this study at any time.

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.

CONSENT:
I have read all of the above, asked questions and received satisfactory answers about what I did not understand. I agree to take part in this research study. I will be given a signed copy of this consent form for my records.

_____
Name of Patient (Please Print)

_____
Signature of Patient Date

_____
Name of Person Obtaining Consent (Please Print)

_____
Signature of Person Obtaining Consent Date

_____
Translator (only if applicable) Date

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AUTHORIZATION FOR RELEASE
AND DISCLOSURE OF MEDICAL INFORMATION

I agree to take part in this research study. As part of this study, authorized persons from Providence Health & Services Regional Cancer Program will need to collect information from other medical and health care providers to find out how effective and safe the study treatment was for me.

I authorize and direct all of my existing or future physicians and health care organizations who have my medical records including, but not limited to, private practice clinics, hospitals, nursing homes, and home health care agencies, to provide the Providence Health & Services Regional Cancer Program with copies of my medical records as they relate to this study.

In the event of my death, this consent will remain valid. If required by a legal or governing body, I authorize my personal representative or family member to fill out any additional forms necessary to confirm my consent for the release of my medical records/information.

Information obtained by the Providence Health & Services Regional Cancer Program will be used only in connection with this research study.

This consent to release medical records will stay in effect unless I change my mind. A copy of this release will be as valid as the original.

_____

Patient Signature Date

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