COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

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

Study Title: Single Arm Neoadjuvant Phase I/II Study of MEDI4736 (Anti-PD-L1 Antibody) Concomitant with Weekly Nab-paclitaxel and Dose Dense Doxorubicin/Cyclophosphamide (AC) Chemotherapy for Clinical Stage I-III Triple Negative Breast Cancer

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Invitation to Participate and Description of Project

You are invited to take part in a research study because you have clinical stage I-III, triple negative breast cancer that may benefit from preoperative chemotherapy. The research study is designed to test if adding a new drug, MEDI4736 that increases the activity of the immune cells present in the cancer tissue, increases the anti-cancer activity of the current standard of care chemotherapy including Nab-paclitaxel given once every week x 12 treatments followed by doxorubicin and cyclophosphamide given once every 2 weeks x 4 treatments. The study will also test the safety of this combination therapy.

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

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

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

The research study is being sponsored by AstraZeneca, the maker of MEDI4736. AstraZeneca, Yale University is being paid by AstraZeneca to conduct this research study. Dr. Lajos Pusztai is the principal investigator of this study at Yale Cancer Center. The study doctors will not get financial payment for any specific results from this study.

Purpose

The first phase of the study including 3-12 subjects will assess if a new immunotherapy drug, MEDI4736, can be given safely with the standard of care chemotherapy (Nab-paclitaxel followed by doxorubicin and cyclophosphamide) before surgery for breast cancer. The second phase of the study including 24-55 subjects will assess the anticancer activity of MEDI4736 administered together with chemotherapy before surgery. The anticancer activity is measured by how often the study drug combination eradicates the cancer completely from the breast and lymph nodes (meaning that invasive cancer is no longer found at the time of the surgery). The study will also test the safety of this combination therapy.

The study drug that will be used in this clinical trial, MEDI4736, is an investigational drug. This means it has not been approved for use by the United States Food and Drug Administration (FDA) to treat cancer.

MEDI 4736 is designed to increase the activity of immune cells that can fight cancer. These cells may cause inflammation within the tumor, as well as within normal tissues. Therefore, by taking MEDI 4736, you may develop inflammatory or autoimmune reaction against the cancer as well as against parts of your own body. There have been ongoing clinical studies in different cancer types exploring the anticancer effect of MEDI4736 but this is the first clinical study that will assess its anti-cancer activity and side effects when it is given together with chemotherapy.

All treatments other than MEDI4736 that you will receive during this clinical trial are considered standard of care. Tests and procedures that would be performed for your regular cancer care in the absence of participating in a clinical trial are called “standard of care.” All of the tests and procedures listed below that will be performed during this clinical trial are standard of care unless noted with an asterisk (*).

If you agree to participate, you will receive 20 weeks of chemotherapy with MEDI4736 before surgery. Subsequently, you will undergo surgery to remove any cancer from your breast and axillary lymph nodes.

Up to 61 subjects will take part in this study.

Tests and procedures before starting therapy

If you agree to take part in this study, you will be asked to do the following:

You will need to undergo a series of tests and procedures to determine if you are eligible to participate in the research study. If you have had some of the required tests performed recently, they may not need to be repeated; this will depend of the date of the exam.

- Medical history and complete physical exam including your breasts and regional lymph nodes.
- Bilateral mammograms. You may also need ultrasonogram or MRI of the breast and regional lymph nodes if your physician considers it clinically important. If the tumor is not palpable and is less than a size of a quarter, marker clip may need to be placed in the breast to identify the cancer for surgery.
- CT scans of the chest, abdomen, pelvis and a bone scan or PET-CT may be needed to assess if the cancer has spread beyond the breast and lymph nodes. Your physician will decide if you need these tests or not.
- Blood tests to measure your blood counts, the clotting ability of your blood and your kidney and liver functions as well as electrolytes in your blood.
- Pregnancy test for women of childbearing potential. Subjects must have a negative urine or serum pregnancy within one week prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Subjects with abnormal liver functions or clinical symptoms or history of hepatitis will also have blood tests to rule out acute hepatitis (e.g. HAV Ab; HBsAb; HBsAg; HBcAb; HCV Ab). (*)
    - Positive hepatitis test results must be reported to the Department of Health as per Connecticut State Law. If you do not wish to have a positive hepatitis test result reported to the Department of Health, you should not participate in this research study.
- You will also be asked to undergo a biopsy of the breast cancer to get tissue specimen for research before you start pre-operative chemotherapy. To get these samples, a core biopsy needle will be inserted into the tumor after the skin has been numbed with local anesthetic. This procedure is very similar to your original breast biopsy that was performed to find out the diagnosis. Three to four small samples of the tumor will be removed in one biopsy session. The biopsy will be performed by a physician who performs these procedures routinely at Yale Cancer Center. (*)
- A blood test called TSH hormone level measurement (and free T4 if TSH is elevated) to asses thyroid function. (*)
- Approximately 10 cc (two tablespoon) of blood will be drawn for future research studies. (*)
- Electrocardiogram (ECG). (*)

Tests and procedures during the treatment period

If the above assessment shows that you can be in the study, and you choose to take part, then you will need the following tests and procedures.

- Before each chemotherapy you will need to have a test called complete blood count to check the number of red blood cells, white blood cells, and platelets in your blood. This will be done once a week during weekly treatments and once every 2 weeks during every 2-week treatments (see section below on treatment). Results from this test will determine if you can receive chemotherapy on that day or a treatment needs to be delayed.
- Before, during and for 1 hour after administration of chemotherapy and MEDI4736 you will evaluated by the chemotherapy infusion nurse.
- Every 2 weeks during treatment you will have a clinic visit with your physician who will review your medical history, including all drugs that you take and perform physical examination.
- Every 4 weeks during your treatment you will also have blood tests to measure your blood counts, the clotting ability of your blood and your kidney and liver functions as well as electrolytes in your blood.
- The thyroid hormone level (TSH) will also be checked every 4 weeks. (*)
- The electrocardiogram will be repeated on weeks 6 and 17 after starting therapy. (*)

Non-sterilised male patients who are sexually active with a female partner of childbearing potential and female patients of childbearing potential who are sexually active with a non-sterilised male partner must use a combination of 2 methods of effective contraception from screening, and must agree to continue using such precautions for 6 months after the final dose of MEDI4736 and AC chemotherapy. It may be safer not to become pregnant even up to one year after you stop taking the study drugs. Females of childbearing potential are defined as those who are not surgically sterile (i.e., had bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Effective methods of contraception are listed in the table on the next page.

Effective methods of contraception (a combination of two methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Male condom plus spermicide • Cap plus spermicide • Diaphragm plus spermicide	• Copper T • Progesterone T • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

Treatment during this study

The first 3 subjects treated on this study will receive MEDI4736 at a dose level of 3 mg per kilogram body weight, in combination with the standard of care chemotherapy. If there is no significant concern for side effects at this dose, the dose of MEDI4736 will be increased to 10 mg per kilogram for all subsequent subjects.

The safety and effectiveness of the study drug will also be assessed after the first 22 subjects have completed therapy, if there are no serious safety concerns and there is no indication that the effectiveness of therapy is low, the study will enroll a maximum of 61 subjects.

All subjects will receive chemotherapy treatment which is standard of care. You will also be given anti-nausea medications and additional medicines to reduce the risk of allergic reactions to drugs before each chemotherapy. The duration of each treatment session lasts between 1.5 – 4.0 hours. All drugs in this study are given through a needle in your vein (intravenously). You will need to have a central venous access, a catheter or port inserted in a large vein, in order to receive therapy. You and your physician will decide together what catheter is most convenient for you.

The exact dose and schedule of your study drug combination is included in the table below:

DRUG	DOSE	ROUTE	FREQUENCY OF ADMINISTRATION
MEDI4736 (*)	In the first stage will start at a dose 3mg/kg, with a plan to increase to 10mg/kg in the second stage	through the veins	Once every 2 weeks x 20 weeks (10 times total)
Nab Paclitaxel	100mg/m2	through the veins	Once every week x 12 weeks durings weeks 1-12 (12 treatments total)
Doxorubicin	60 mg/m2	through the veins	Once every 2 weeks during weeks 13-20 (4 treatments total

Cyclophosphamide	600 mg/m^2	through the veins	Once every 2 weeks, during weeks 13-20 (4 treatments total)
Pegfilgrastrim	6 mg	Injected under the skin	Once every 2 weeks, One day after the chemotherapy during weeks 13-20 (4 treatments)

The total duration of treatment is 20 weeks. During the first 12 weeks (weeks 1-12) you will receive Nab-paclitaxel (also called Abraxane) chemotherapy once a week for 12 treatments concomitant with every other week MEDI4736 (weeks 1, 3, 5, 7, 9, 11) on the same days as the Nab-paclitaxel.

After completion of the Nab-paclitaxel phase of the therapy, you will receive doxorubicin (also called Adriamycin) and cyclophosphamide (also called Cytoxan) each given once every 2 weeks (14 days) for 4 treatments. MEDI 4736 will be given once every 2 weeks, one day after the Doxorubicin and Cyclophosphamide infusion. On Day 2 of each Doxorubicine/Cyclophosphamide chemotherapy immediately before the administration of MEDI4736 you will also receive an injection under the skin with pegfilgrastrim (also called Neulasta). Pegfilgrastim is given to increase bone marrow recovery after chemotherapy and is standard of care therapy.

After completion of chemotherapy + MEDI4736

Approximately 10 cc (two tablespoon) of blood will be drawn for future research studies approximately two weeks after completion of all chemotherapy but before surgery. (*)

Surgery will be performed after completion of the last chemotherapy usually within 4 weeks. You and your surgeon will decide together what the most appropriate surgery is for you. You may have your whole breast removed (mastectomy) or only parts of the breast that contained cancer (lumpectomy). All subjects will have sampling of the lymph nodes in the axilla (arm pit) during the breast surgery.

In subjects who have invasive cancer at the time of surgery, after the pathologist have examined the cancer that was removed during surgery, a piece of the cancer will be collected for research. (*) The research will include examining immune cells in the cancer and the genes of the cancer that survived the chemotherapy. The research will also involve studying the structure of genes that regulate the immune system.

Follow up period:

Three follow-up visits will be performed after completion of therapy to assess your recovery from the experimental drug combination. During these visits complete medical history and physical examination will be performed and blood tests will be done to assess your blood count and liver functions.

The first visit is 2 weeks (+/- 1 week) after completion of the last MEDI4736 therapy.

The second visit is 6 weeks (+/- 1 week) after completion of therapy (approximately 2 weeks after surgery).

The third, last visit on study, is 13 weeks, approximately 90 days (+/- 14 days), after completion of therapy. (*)

How long will I be in the study?

Your study treatment period will last for 20 weeks and your study participation will end with a final study visit approximately 90 days after completion of your surgery.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the treating physician, your study doctor, if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from stopping early can be discussed with you by your study doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest or if you do not follow the study rules; or if the study is stopped.

Potential Risks, Side Effects, Discomforts and Inconveniences

You may have side effects while on the study. 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 will give you medicines to help lessen side effects. Many side effects go away soon after the completion of this experimental chemotherapy combination. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study. This is very important to do, even if the side effects are occurring in between your visits with the study doctor, because if you are having side effects the dose of the drugs may need to be reduced or the experimental drug combination held.

There is small risk (2-3%) that your cancer may continue to grow despite receiving this experimental combination. Your doctor will closely follow your cancer by physical exam and order repeat mammogram or ultrasonogram if necessary. If the cancer grows, you will discontinue therapy and may undergo surgery to remove the cancer or could receive other treatment.

Risks and side effects related to MEDI4736

MEDI4736 is an investigational drug that has only been studied in limited number of subjects and not all side effects may be known. The most important possible side effect of this experimental therapy is the increased risk for autoimmune diseases, your own immune system attacking your own body. These could include inflammation of the bowel, skin, lung, liver, kidneys and nerve cells or hormonal glands such as problems with the thyroid gland and it is hormone production. Some of the side effects may occur during the infusions or after infusions (within hours to days after). The side effects usually get better without treatment. However, if left untreated, some may become serious or life-threatening.

Side effects that may be experienced as a result of the immune system's reaction to medications that activate the immune system include the following:

- Fever
- Fatigue
- Rash or hives with or without itchiness and swelling
- Change in blood pressure that is sometimes significant
- Decrease in blood platelets (cells that stop bleeding) with symptoms such as unexpected bruising, bleeding from the nose or gums, blood in vomit or stools or red spots under the skin
- Inflammation of the lungs with symptoms including difficulty breathing
- Inflammation of the nervous system with symptoms including a tingling or burning feeling, sharp pain, weakness, numbness or reduced ability to feel pain and temperature changes especially in the fingers and toes and pain while walking
- Inflammation of the pancreas with symptoms such as abnormal laboratory blood tests, stomach pain, nausea, vomiting and tenderness when touching the stomach
- Inflammation of the liver with symptoms such as stomach swelling, bloating, diarrhea, discolored urine or stools, loss of appetite, tiredness, nausea with or without vomiting, yellowing of the skin and whites of the eyes. Increases in the blood level of substances called enzymes found within your liver cells may occur. The enzyme changes are unlikely to make you feel unwell.
- Inflammation of the intestines with symptoms such as stomach pain, loose or more frequent stools, blood in stools which may require you to receive additional fluids. If left untreated this may lead to a tear in the wall of the intestine
- Symptoms related to changes in hormone-releasing glands including, but not limited to, increased heart rate, headaches, nausea, vomiting, fatigue, dizziness, weakness, tiredness, mood changes, loss of appetite, weight changes and sexual dysfunction
- Inflammation of the kidneys with symptoms such as abnormal blood tests, changes in urinary volume and pain in the abdomen
- Death

Allergic Reactions

There is a chance that you will experience an allergic reaction to MEDI4736. Allergic reactions may be mild (such as skin rash or hives) to severe (such as breathing difficulties or shock). Other

signs of an allergic reaction might include, but are not limited to, fever with a rash and swelling of the face or tongue. A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. You should report any signs of an allergic reaction to your study doctor or nurses as soon as possible or seek immediate medical attention for severe symptoms.

The following side effects were seen with administration of MEDI4736 to 694 subjects with various types of cancer in clinical trials:

Likely (expected to occur in 10% to 25% of people):

- Fatigue (which may be serious)

Less likely (expected to occur in 2% to less than 10% of people:

- Nausea (which may be serious)
- Diarrhea (which may be serious)
- Decreased appetite
- Itchiness
- Rash
- Vomiting (which may be serious)
- Low thyroid
- Joint pain (which may be serious)
- Increased liver enzymes (which may be serious)
- Muscle pain
- Difficulty breathing (which may be serious)
- Fever
- Cough
- Low red blood cell count
- High thyroid
- Weakness

Rare but serious (expected to occur in <1% of people):

- Fluid in the space surrounding the lung
- Inflammation of the lung
- Lung infection – Reported in one subject and resulted in death
- Inflammation of the large intestine
- Inflammation of the tube that leads to the large intestine
- Blockage in the small intestine
- Failure of the adrenal glands to produce enough steroid hormones
- Low white blood cell count

- Lack of muscle control during walking or picking up objects
- Dehydration
- Sudden decrease in kidney function
- Elevated level of glucose (sugar) in your body
- Central nervous system inflammation
- Abnormal heart rhythm
- Swelling of the tumor
- Bleeding in the upper portion of the gastrointestinal tract

Risks and side effects related to the Nab-paclitaxel treatment include the following:

Likely (occurring in > 20% of people):

- Fatigue
- Hair loss
- Numbness, tingling in hands and/or feet (neuropathy). These symptoms of neuropathy usually get better or go away entirely after stopping treatment.

Less Likely (occurring in < 20% of people):

- Nausea (feeling as if you're about to throw up) or vomiting (throwing-up)
- Low blood pressure
- Shortness of breath
- Cough
- Inflammation or irritation of the mucous membranes in the mouth or throat.
- Heart burn
- Diarrhea – increased frequency of bowel movements with loose, watery stool
- Low white blood cell counts, which may make you more susceptible to infection
- Low platelet counts, which may make you bruise more easily and bleed longer if injured
- Low red blood cell counts, which may cause tiredness, shortness of breath or fatigue
- Abnormal blood tests reflecting problems with liver function
- You may get joint and muscle pain a few days after your treatment. These symptoms usually disappear in a few days.
- Skin rash
- Nail changes

Rare but serious (occurring in < 1% of people):

- Liver failure including brain and nervous system damage that occurs as a complication of liver disorders.

- Serious, sometimes life threatening gastrointestinal (GI) perforations have occurred rarely. A GI perforation is the development of an opening or hole in the wall of the bowel or stomach that may require surgery to repair.

Risks and side effects related to the doxorubicin and cyclophosphamide treatment include:

Likely (occurring in > 20% of people):

- Fatigue
- Hair loss
- Low white blood cell counts, which may make you more susceptible to infection
- Low platelet counts, which may make you bruise more easily and bleed longer if injured
- Low red blood cell counts, which may cause tiredness, shortness of breath or fatigue

Less Likely (occurring in < 20% of people):

- Nausea (feeling as if you're about to throw up) or vomiting (throwing-up)
- Sores in the mouth
- Heartburn
- Tingling pain and redness of the hands and feet (Hand-foot syndrome)
- Change in color of fingernails and toenails
- Loosening of fingernails and toenails
- Inflammation or damage to the skin and around the IV tubing.
- Bone or joint pain
- Cramps in the legs or back

Rare but Serious (occurring in < 1% of people):

- Increased risk of heart damage including weakness of heart muscles that prevent the heart from pumping blood normally and could be life threatening
- Blood cancer (leukemia)

Irritation at the Chemotherapy Infusion Site:

Chemotherapy may cause irritation and tissue damage at the site of injection. These reactions are caused by the intravenous fluid that contains chemotherapy leaking into the surrounding area. Reactions may include pain, redness, swelling of the surrounding skin or of the vein itself, and ulceration of the skin (open sores). If you notice anything unusual at the site of the injection (where the needle is inserted), either during or after treatment, tell your nurse right away who will notify your study doctor.

Other instructions

Tell your study doctor about all of your medicines. Include prescription medicines, over the counter drugs, vitamins, and herbal products. Some medicines can react with the study drugs that you receive and may cause serious side effects.

Keep a list of your medicines, and show it to your study doctor or pharmacist. Talk to your study doctor before starting any new medicines.

Reproductive risks:

You cannot participate in this study if you are pregnant.

You should not plan to become pregnant or father a baby while on this study or within 120 days from completion of the experimental drug combination because the drugs in this study can affect an unborn baby and cause serious birth defects.

Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. You also should not donate egg cells while you are receiving the study drug.

Check with your study doctor about what kind of birth control methods to use and how long to use them. If you become pregnant while participating in this study, inform your study doctor immediately.

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 your study doctor.

Risks associated with procedures during this study:

Placement of either an intravenous (IV) line or port-o-cath:
Placement of an intravenous catheter or port is routine for chemotherapy administration. There is a slight chance that multiple needle-sticks may be necessary to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed. A bruise or an infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated with outpatient antibiotics but rarely may require hospital admission. A blood clot may develop in the vein where the intravenous line is placed.

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 (2-3 tablespoons) of blood will be taken during your participation in this research study for research purposes only.

Breast cancer biopsy for research:
Biopsies may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsy. An allergic reaction to the anesthetic that is used to numb your skin before the biopsy may occur. A scar may form at the biopsy site. Standard precautions will be used and every effort to minimize these risks will be taken. Biopsy-related complications will be treated following standard clinical practice and will be charged to you/your insurance company as standard clinical service. Removing some cancer tissue with the research biopsy, may also make the exact size determination of your cancer less precise after surgery.

Risk that your protected health information could be misused:
We expect that there will be widespread sharing of the research biopsies collected before starting therapy or from the cancer that was removed during surgery and the molecular data and associated information among breast cancer researchers within Yale University and in other academic or commercial research laboratories. When your specimens and information are stored and shared in the process of research, we are careful to try to protect your identity from discovery by others. Your stored tissue, genetic and molecular data will only be labeled with a code. Other researchers will only receive coded samples and information, and will not be able to link the code to you. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Your research chart will contain your personal medical information. This chart will be kept in a locked file cabinet in the research coordinators office. If your stored specimens are shared with other investigators for any reason, no personal identifiers will be included. The key linking stored samples with your personal information will be maintained separately by the designated research personnel who are responsible for collecting the clinical information. Some molecular data will be deposited into a public database as customary and required for scientific publications. This data will be de-identified, meaning it will have no name or code. There will be no way of linking you to the data.

This research may also identify variants of genes in your normal tissues (blood or normal breast samples) that can raise the suspicion that you are at high risk to develop cancer or other diseases in the future. This risk may also extend to your blood relatives. This knowledge could lead to stress, anxiety and may require further diagnostic tests and other medical interventions to confirm the result.

It is important that you understand that:
(i) Genetic changes detected in cancer tissue provide limited information about inherited disease causing gene variants, but changes detected in normal tissues such as your blood or normal breast samples can raise the suspicion for inherited disease causing gene variants.

(ii) The list of gene variants that are associated with diseases constantly changes over time and there will be no efforts to systematically search for disease causing gene variants in your data at any time.

(iii) Your tissues will be used for research and not for routine clinical testing. Therefore, the tests performed on your normal samples cannot establish the diagnosis of a disease or be used to measure your risk to develop a disease. However, findings may raise the suspicion that you carry a disease-causing variant.

(iv) Testing of your samples may be performed several years after the tissue was collected.

(v) Test results particularly those performed by collaborators in other laboratories may not be fully communicated to the Principal Investigator (Lajos Pusztai, MD. DPhil).

If you decide to withdraw your consent to the use of donated samples, the samples will be disposed of/destroyed, and the action will be documented. In case the Principal Investigator becomes aware of research results that raise the suspicion that you have a disease causing gene variant, you have the option to be notified, or not, of these results. If study results are communicated to you, you will receive the information from your treating physician or the Principal Investigator during a follow-up visit. During the visit, you will have the opportunity to ask questions and will be provided with the necessary support and referrals to genetic counseling and to a laboratory certified for clinical genetic testing to confirm the research test results. There is a possibility that the research results may not be confirmed by an approved clinical diagnostic tests and the research result is a “false alarm”. Very rarely, health or genetic information could be misused by employers, health insurance companies, and others. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers (except those with fewer than 15 employees) 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.

If research on your normal tissues raises the suspicion that you may have an inherited disease causing gene, when this information becomes available for the Principal Investigator do you want to be informed about it?

☐YES _____ ☐NO _____

Patient Signature Patient Signature

If you chose to be informed about the suspicion about a disease-causing gene, all reasonable efforts will be made to contact you through phone or mail as soon as the suspicious results become available to the Principal Investigator. A designated person will reach out to you to set up a physician appointment to discuss the research result and what to do next. However, research findings may become available only several years after you donated your tissue. If you moved in the meantime and if we are unable to find your new address it may not be possible to reach you.

Benefits

During this clinical trial you will receive one of the currently most effective chemotherapies for triple negative breast cancer (Nab-paclitaxel and Doxorubicin and Cyclophosphamide) and in addition you will also receive a new immune system activator, MEDI4736.

While doctors hope this combination will be more useful against cancer compared to the best current treatment, there is no proof of this. 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 study will benefit other patients with breast cancer in the future.

Economic Considerations

You will not be paid for taking part in this study.

There will be no charge to you or your insurance provider for the MEDI4736 which will be provided by AstraZeneca, the pharmaceutical company that makes MEDI4736, free of charge.

The chemotherapy drugs Nab-Paclitaxel, Doxorubicin and Cyclophosphamide are commercially available and considered standard of care and will be charged to you or your insurance company.

There will be no charge to you or your insurance provider for tests or procedures that are performed for study purposes only. These tests and procedures are marked by an asterisk in this informed consent document. The sponsor, AstraZeneca, will pay for the any study related procedures that are not considered standard care for patients with your disease.

All other tests and procedures will be charged to you or your insurance provider in the usual way as these are standard of care. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. You are encouraged to speak with your insurance provider prior to entering the research study to find out your individual coverage.

Treatment Alternatives/Alternatives

Your other choices, if you choose not to take part in this study, may include:

- Receiving the same, or similar, chemotherapy without the experimental drug MEDI4736.
- Receiving no treatment at this time and proceed with surgery for your cancer
- Taking part in another study

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

Confidentiality and Privacy

For purposes of this study, Yale University, Yale-New Haven Hospital, and Dr. 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.

Molecular data and cancer tissue may be shared with other researchers within and outside of Yale Cancer Center. However, your personal information (name, address, medical record number, etc.) will not be shared with any outside research personnel. Your samples and information will receive a unique study subject code. Other researchers will only receive coded samples and information, and will not be able to link the code to you and your personal information. Molecular data from the cancer may be deposited into a public database as required for scientific publications; these data will not include any personal information and there will be no way of linking it to you.

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, diagnostic scan results, pregnancy tests, 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 infectious diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.
We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the study staff will get information that identifies you and your protected health information. This may include information that might directly identify you, such as your name, date of birth, and medical record number. This information will be de-identified prior to providing it to the sponsor, meaning we will replace your identifying information with a code that does not directly identify you. The study doctor will keep a link that identifies you to your coded information, and

this link will be kept secure and available only to the Principal Investigator or selected members of the study team. Any information that can identify you will remain confidential

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

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, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee 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.
- Those providers who are participants in the Electronic Medical Record (EMR) system
- 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.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments.
- The Principal Investigator: Lajos Pusztai, MD, DPhil, and the Yale study team
- AstraZeneca. (the study sponsor)
- Health care providers who provide routine or research services to you in connection with this study.
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Study collaborators and other investigators.
- Study Coordinator and Members of the Research Team
- 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 the Yale School of Medicine, Yale-New Haven Hospital, and the Smilow Cancer Center are 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, AstraZeneca, may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others.

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

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, you will not be allowed to look at or copy your study related information until after the research is completed.
This authorization to use and disclose your health information collected during your participation in this study will never expire.

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.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

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 study related appointments.

The study doctor may decide to take you off this study if your disease gets worse despite the study drug combination; if the side effects of the study drug combination are too dangerous for you; or if new information about the study drug combination becomes available and this information suggests the study drug combination will be ineffective or unsafe for you. It is unlikely, but the study may also be stopped early due to lack of funding.

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 doctors or with Yale School of Medicine, Yale New Haven Hospital, the Smilow Cancer Center, or Saint Francis Hospital and Medical Center. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor of your choice.

If you fail to give your consent by not signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any drug or procedures 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 Lajos Pusztai at the address listed on the next page.

Lajos Pusztai M.D. (Medical Oncology)
Yale University Cancer Center
Smilow Cancer Hospital
Section of Medical Oncology
333 Cedar St., PO Box 208032
New Haven, CT 06520-8032
Tel: 203-737-8309
Fax: 203-785-5792

If you withdraw your permission, you will not be able to stay in this study.

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

Questions

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

Authorization and Permission

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

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

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

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

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

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Lajos Pusztai, MD, DPhil 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.