PRINCIPAL INVESTIGATOR: Fatima Karzai, MD

STUDY TITLE: A Phase Ib Trial of Sequential Combinations of BN-Brachyury, Entinostat, ado-trastuzumab emtansine and M7824 in Advanced Stage Breast Cancer (BrEAsT)

STUDY SITE: NIH Clinical Center

Cohort: *Affected Participants*

Consent Version: *07/06/2021*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have been diagnosed with metastatic breast cancer, such as Triple Negative Breast Cancer (TNBC) or ER-/PR-/HER2+ Breast Cancer (HER2+BC).

The purpose of this research study is to determine if a combination of immunotherapy drugs is effective in patients with metastatic breast cancer. Everyone on the study will receive the BN Brachyury vaccine and M7824. T-DM1 with or without Entinostat may be added in participants with HER2+ BC. These drugs are designed to help the immune system fight cancer.

T-DM1 has been approved by the FDA specifically for the treatment of HER2-positive metastatic breast cancer (mBC) in patients who previously received trastuzumab and a taxane (paclitaxel or docetaxel), separately or in combination. The use of BN-Brachyury, Entinostat, and M7824 in this study is considered investigational, which means that the use of this combination has not been approved by the U.S. Food and Drug Administration (FDA) to treat metastatic breast cancer. However, the FDA has given us permission to use the combination of BN-Brachyury, Entinostat, M7824, and T-DM1 in this study.

There are other drugs that may be used to treat your disease, and these can be prescribed/given by your regular cancer doctor, even if you are not in this study.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- We will first perform some tests and procedures to find out if you meet the study requirements. We will also confirm the status of your disease. You must have already received treatment for this cancer, for some groups you may need to have already received treatment for this cancer with a taxane (docetaxel or paclitaxel), Herceptin, and pertuzumab.
- Study treatments will be given based on your type of cancer and when you enroll in the protocol. The three possible treatment groups or arms are:
    - Arm 1: (TNBC) BN brachyury + M7824
    - Arm 2 (HER2+ BC): BN brachyury + M7824 + T-DM1
    - Arm 3 (HER2+ BC): BN brachyury + M7824 + T-DM1 + Entinostat
- The first 6 participants with TNBC will be directly assigned to Arm 1. If there are no intolerable side effects in this group, we will begin to enroll patients with HER2+ BC for Arm 2. We will continue to enroll TBNC participants into group 1 until 8-13 patients are enrolled. After 6 HER2+ patients have been tested for side effects in Arm 2, the next 6 will be enrolled into Arm 3. Once it is known that the combination in Arm 3 is safe, the remaining HER2 patients will be enrolled by direct alternating assignment to Arm 2 or Arm 3. An equal number of participants will be assigned to Arms 2 and 3.
- You will receive treatment for as long as you are benefiting from it. Each treatment will be given in the Oncology Outpatient Center and will take approximately 2-4 hours. This allows time to give the treatment and monitor you before and after.
    - BN-Brachyury is a combination of MVA-BN Brachyury and FPV-Brachyury vaccines. The vaccines will be given once every three weeks, on the same day you receive M7824 and, if you are assigned, T-DM1. After cycle 9, BN-Brachyury vaccines will be given to you every 12 weeks.
    - MVA-BN Brachyury will be given in four injections under the skin at different sites on your body. You will only receive this vaccine during your first two treatments.
    - FPV-Brachyury will be given in a single injection under the skin each cycle, starting with cycle 3.
    - M7824 will be given by intravenous (IV) infusion (a needle inserted into a vein allowing the solution to be given over a period of time) once every three weeks for up to 12 months. The infusion will take approximately one hour, but could take more or less time.
        - If you are assigned to Arm 1, there will be an observation time period where you will be monitored for up to an additional 60 minutes after your M7824 infusion is complete.
    - T-DM1 will be given by IV infusion once every three weeks. The first infusion will take approximately 90 minutes and later infusions will take approximately 30 minutes, but these could take more or less time.
        - If you are assigned to Arm 2 or 3, there will be an observation time period where you will be monitored for up to an additional 90 minutes after your T-DM1 infusion is complete as recommended by the FDA.

- Entinostat will be taken by mouth, in tablet form, on a weekly basis. On the days when you receive infusions, this will be taken around bedtime on the day of the infusion.

- You may experience side effects from taking part in this study. Some can be mild or temporary, but others may be serious, long-lasting, or permanent, and may include death. Examples of some of the side effects that you may have include: injection site reaction, fatigue, headache, nausea, diarrhea, chills, shortness of breath, anemia, high blood sugar, decreased sensation of your hands/feet, bleeding of your gums or from your nose. A more complete list of possible side effects is described later in this consent. It is important that you read and understand the possible risks.
- M7824 is a new immunotherapy drug and although it may cause similar side effects of other immunotherapy agents, it has also been found to cause additional skin problems, different problems with the immune system, low red blood cell count (anemia) and bleeding. It is possible that the anemia and/or bleeding may be so severe that you require a blood transfusion. You cannot join this study if you are not willing to have a blood transfusion.
- You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and to see if your disease is responding to the treatment. We will also collect required samples from you (such as blood and tumor biopsies) for both clinical and research purposes.
- After the study treatment has ended, we will contact you for long term follow-up every 3 months for one year and then every 6 months for one additional year to ask about any adverse events you have experienced and further treatment of your tumor for a total of 2 years. We will also take scans if your tumors have not grown or spread during this time.

Just as we do not know what side effects that you might have, we cannot know if you may benefit from taking part in this study. If you do not benefit, this study and the results from our research may help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to determine if a new combination immunotherapy is effective in shrinking tumors in patients with metastatic breast cancer.

We are asking you to join this research study because you have been diagnosed with metastatic breast cancer, such as Triple Negative Breast Cancer (TNBC) or ER-/PR-/HER2+ Breast Cancer (HER2+BC).

T-DM1 has been approved by the FDA specifically for the treatment of HER2-positive metastatic breast cancer (mBC) in patients who previously received trastuzumab and a taxane (paclitaxel or docetaxel), separately or in combination. BN-Brachyury, Entinostat, M7824 and T-DMI are considered investigational, which means that the use of this combination has not been approved by the U.S. Food and Drug Administration (FDA) to treat metastatic breast cancer.

WHAT WILL HAPPEN DURING THE STUDY?

Below is a description of what will be asked of you and what will occur if you decide to take part in this study.

Before you begin the study

To determine if you can be a part of this study, you will need to have the following tests and procedures: Medical history and physical examination including height, weight, and vital signs;

- Routine blood tests;
- Hepatitis B and C screening tests;
- HIV screening test;
- Pregnancy test for women who are able to have children;
- CT scan of the chest, abdomen and pelvis and/or MRI ;
- MRI/CT of the brain;
- Echocardiogram, a test to create images of the heart;
- Electrocardiogram (EKG), a test to measure the electrical activity of the heartbeat; and
- Confirmation of your disease. If there is no available tumor sample or pathology report, a biopsy will be performed to confirm the diagnosis.
- Measuring oxygen levels in your body

During the study

Once we know that you are eligible and you sign the consent document agreeing to participate in the study, you may need to have some of the tests that were done at screening repeated, depending on how much time has passed. Your study team will let you know if any of the above tests need to be repeated.

During your participation you will receive a combination of BN-Brachyury, Entinostat, M7824, and T-DM1. Your specific combination of these drugs will depend on the group you are assigned to as described above in Key Information About This Research. The study drugs will be given in cycles, with each cycle lasting 3 weeks. After one year, M7824 will be discontinued, but the other study drugs will be continued per the group in which you are enrolled until you are no longer benefiting from study therapy.

- BN-Brachyury is a combination of MVA-BN Brachyury and FPV-Brachyury vaccines. The vaccines will be given once every three weeks, on the same day you receive M7824 and, if assigned, T-DM1. After cycle 9, BN-Brachyury vaccines will be given to you every 12 weeks.
  - You will receive MVA-BN Brachyury in four injections under the skin at different sites on your body. The preferred injections sites include the left upper arm, the right upper arm, the left outer thigh, and the right outer thigh. MVA-BN-Brachyury is given the first and second cycles only.
  - You will receive FPV-Brachyury in a single injection under the skin. FPV-Brachyury is given starting the third cycle.
- You will receive M7824 by IV infusion once every three weeks for up to 12 months. The infusion will take approximately one hour but could take more or less time. Before your M7824 infusion you may receive standard pre-medication of an antihistamine like Benadryl and acetaminophen (Tylenol). If you have a preexisting titanium central line, then M7824 may be able to be administered through the central line in place of an IV infusion.
  - If you are assigned to Arm 1, there will be an observation time period where you will be monitored for up to an additional 60 minutes after your M7824 infusion is complete.
- If assigned to Arm 2 or 3, you will receive T-DM1 by IV infusion once every three weeks. The first infusion will take approximately 90 minutes and later infusions will take approximately 30 minutes, but these could take more or less time.
  - If you are assigned to Arm 2 or 3, there will be an observation time period where you will be monitored for up to an additional 90 minutes after your T-DM1 infusion is complete as recommended by the FDA.
- If you are assigned to Arm 3, you will take Entinostat by mouth, in tablet form, on days 1, 8 and 15 of each cycle. It should be taken on an empty stomach (at least 2 hours after a meal and 1 hour before the next meal). If you forget to take a dose on the assigned day, you can take it up to 24 hours later. On day 1 of each cycle, you should take Entinostat at around bedtime on the day of the infusion. On day 8 of cycle 1, please take it in the morning before you come to the clinic. If you will have bloods drawn on day 15 of cycle 1 (this is optional), please take it in the morning on that day as well.

  At the start of each cycle, we will give you enough entinostat for a cycle. We will also give you a pill diary so you can keep track of the times you are taking Entinostat. At each clinic visit, please bring your pill diary and any pills you might have left over.

  Do NOT split, crush or chew entinostat tablets. If you vomit after swallowing the entinostat, you should not take the dose again unless you can see the tablet in your vomit and the tablet is still in one whole piece. You should discuss with the study team before you re-take your dose.

We will continue to take assessments, such as physical exam, weight, vital signs, EKG and/or echocardiogram, collection of blood for testing, pregnancy test for women of childbearing potential, and scans for evaluation of your tumor during your participation.

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of

research only. The samples are being tested to find out how your body processes the study drugs, find out whether or not your body creates antibodies (proteins) that attack the study drug, and look at the effects of therapy on your immune system and markers of tumor activity, including collecting and testing tumor cells.

The samples included for these studies include:

- Blood Tests, weekly during cycle 1 (day 15 of cycle 1 is optional); day 1 of cycles 2, 3, 5 and 6 and at the end of your treatment.
- Tumor Biopsy, collected before you have taken any study drug, on day 1 of cycle 3. If you are enrolled on Cohort 3 (after it is known that the combination in Arm 3 is safe), the biopsy will be required. It is optional if you are enrolled prior. Your study doctor will let you know which group you are in.
- Tumor Block, collected on C1D1 before you have taken any study drug.

In this study, we will perform genetic testing on your DNA and RNA. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. RNA (ribonucleic acid) carries instructions from your DNA to the parts of the cells that makes proteins. We will perform limited genetic testing on certain immune cells in your blood and tumor samples to characterize changes in the DNA of a particular molecule located on the immune cell. We will perform further genetic testing on your blood samples, looking at how much RNA you have for certain panels genes. This helps us to learn how active the genes are.

When you are finished with treatment

End of Treatment Visit

If you stop participation in the study before the completion of one year of treatment, then you will be asked to come into the clinic on the day of or within 30 days of the decision to stop treatment for the following tests and procedures: physical examination including weight and vital signs; routine blood tests; pregnancy test if you are a woman who can have children; scans if you stop study therapy before your disease worsens and an optional tumor biopsy. The optional biopsy will only be taken at the time your disease gets worse. You will be asked to sign a separate consent at the time of the biopsy if you agree to have it done. It is possible that your disease may not have gotten worse at the time of this visit. If not, the optional biopsy will be requested at a later visit.

Safety Visit

After your treatment ends or if you stop participation in the study for any reason, you will be asked to come into the clinic for a 28-day follow-up visit or telephone call following your last dose of study drug(s).

During the visit the following tests and procedures will be given: physical examination including weight and vital signs; routine blood tests; pregnancy test if you are a woman who can have children; and if your disease has worsened an optional tumor biopsy may be requested if we have not already collected one.

Long Term Follow-up

We will also contact you for long term follow-up every 3 months for one year and then every 6 months for one additional year.

If your disease has progressed while being treated then you will be followed by phone or email for any adverse events you may have experienced and further treatment of your tumor for two years. If your disease has worsened an optional tumor biopsy may be requested if we have not already collected one.

If your disease did not progress while being treated then you will receive tumor scans until progression of your disease and will be followed by phone or email for any adverse events, and further treatment for two years.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last three years, including approximately one year of treatment and two years of follow-up.

You will be seen multiple times during treatment. You will be asked to come to the NIH weekly to every three weeks depending on where you are in your treatment schedule. Visits usually take about 5-6 hours, but will take no longer than 8 hours.

After the end of treatment, you will start the long-term follow-up part of the study. During this part, you will be contacted every 3 months for one year, then every 6 months for one year.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have up to 65 people total participate on this study at all participating sites.

WE PLAN TO HAVE UP TO 35 PARTICIPATES IN THIS STUDY AT THE NIH. WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

Risks from Study Drugs

Side effects of BN-Brachyury Vaccines
Likely side effects:

- Injection-site reaction (pain or discomfort, itching, redness, firmness, swelling, skin thickening, or bumps)

Less likely side effects:

- Acute fever
- Chills
- Flu-like symptoms (fatigue, soreness, general body pain, abdominal pain, cough, fever, headache)
- Chest tightness
- Shortness of breath
- Leg pain and/or swelling
- Headache
- Loss of appetite
- Weight loss

- Diarrhea
- Constipation
- Rash
- Nausea
- Dizziness
- Mild inflammation of tissue lining the lungs
- Chronic inflammation of the skin
- Difficulty sleeping
- Open sores (ulcers) at the injection site
- Enlarged lymph nodes
- Low blood levels of sodium
- Inflammation of the testicles
- Inflammation of thyroid tissue

Rare, serious side effects:

- Difficulty breathing
- Low blood pressure
- Wheezing
- Clots in the lung
- Clots in the leg
- Kidney damage
- Decreased blood oxygen levels
- Fluid around the lining of the lungs
- Fluid around the lining of the heart

Side effects of Entinostat

Common side effects:

- Fatigue (tiredness)
- Nausea
- Thrombocytopenia (decrease of the blood platelets)
- Anemia (low blood cell count)
- Hypoalbuminemia (low level of albumin in the blood)
- Hypophosphatemia (low serum phosphate concentration)
- Neutropenia / Neutropenic infection (low neutrophils, a type of white blood cells)
- Vomiting
- Anorexia
- Headache
- Diarrhea
- Hyponatremia (low serum sodium concentration)
- Dyspnea (difficulty breathing)
- Dehydration
- Injection site reaction

- Leukopenia (low white blood cell count)
- Hyperglycemia (high blood sugar)
- Hypocalcemia (low calcium levels in the blood)

Side effects of M7824

As a side effect of this experimental therapy, the immune system may target normal tissue. Normal endocrine organs (organs that make hormones) may not work as well leading to tiredness (from low thyroid hormones or adrenal hormones). This may need to be treated by replacement hormones (pills).

Common side effects (occurring in more than 5% of patients):

- Fatigue (tiredness and lack of energy)
- Nausea
- Diarrhea
- Constipation
- Vomiting
- Swelling of you lower legs or hands
- Fever
- Decreased appetite
- Loss of body fluids (dehydration)
- Skin growths called keratoacanthomas that resemble skin cancer. These usually go away after treatment and can leave a scar.
- Rash, blisters, skin discoloration and other skin abnormalities.
- Bleeding has been frequently observed in patients receiving M7824. Patients may experience bleeding in different organs such as gums, nose, ears, eyes, vagina, breast, blood in the urine, stool, or bleeding in the internal organs or skill, coughing up or vomiting blood. Occasionally, this bleeding can be serious and potentially life threatening and require you to receive a blood transfusion. If you experience any bleeding on this trial, please tell the study team immediately. Tell your doctor if you've had a life-long problem of frequent or excessive bleeding or bruising, or if you take aspirin or prescription medication to thin your blood.
- Shortness of breath
- Cough
- Anemia: low number of red blood cells low that can cause tiredness and shortness of breath. May require a transfusion
- Abdominal pain
- Headache
- Itching

Occasional side effects (occurring in less than 5% of patients):

- Chills (feeling cold)

- Blood clots that form throughout the body, blocking small blood vessels. Symptoms may include chest pain, shortness of breath, leg pain, problems speaking, or problems moving parts of the body.
- Easy bruising
- Reaction to other drugs such as rash, anaphylaxis, and changes in blood.
- Infusion-related reaction, including dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.
- Cancerous growth on the skin that can be removed
- Stroke
- Slow wound healing
- Thickening of the skin, nails

Allergic reactions or reactions in the context with the infusions might occur during treatment.

Although M7824 is a fully human protein the risk cannot be completely excluded. In general, these reactions are mild to moderate and can be handled with appropriate drugs, but in very rare cases severe to life-threatening and even fatal reactions might occur, which require advanced cardiac life support.

In addition, immune-mediated side effects might be possible. These side effects are caused by over activity of your body's immune-system. The immune system normally protects you from things that are harmful; such as infections, foreign substances, and sometimes from cancer. If the immune system is overactive, it can attack normal parts of the body because it mistakenly recognizes them as foreign/harmful.

Examples of these side effects are listed below. In rare cases, immune-related side effects can be life-threatening or fatal.

Types of immune related side effects:

- Inflammation in the lungs (pneumonitis): symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients: tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.
- Hypothyroidism (decreased function of the thyroid gland)
- Hyperthyroidism (increased function of thyroid gland)
- Thyroiditis (inflammatory disease of the thyroid gland)
- You may develop inflammation of the liver called hepatitis. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal.
- Thrombocytopenia (decrease of the blood platelets)
- Uveitis (inflammation in the eye)
- Diabetes mellitus (high blood sugar levels)

- Problems with your adrenal glands (Adrenal Insufficiency): may cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement
- Myositis (inflammation of the muscles characterized by pain and tenderness)
- Myasthenia gravis (weakness in the skeletal muscles)
- Inflammation of the intestine (colitis). It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening.
- Autoimmune encephalitis is a type of brain inflammation where the body's immune system attacks healthy cells and tissues in the brain or spinal cord.
- Myocarditis (inflammation of the heart muscle)
- Pemphigoid (fluid-filled blisters that can be itchy)
- Kidney problems: you may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement.
- Pancreatitis (inflammation of the pancreas)
- Liver problems: Increases in the blood level of substances called enzymes found within your liver cells. The enzyme changes are unlikely to make you feel unwell, however, if these blood enzyme levels become very high, your study doctor may need to stop the study medication.
- Nervous system problems: symptoms can include unusual weakness of legs, arms, or face, numbness, or tingling in hands or feet. In rare situations, there is the potential for the inflammation of the nervous system to be severe.

There is a risk of tumor lysis syndrome due to tumor shrinkage. This complication is caused by the breakdown products of dying cells and includes elevated blood potassium, elevated blood phosphorus, elevated blood uric acid and elevated urine uric acid, low blood calcium, and consequent acute kidney failure.

If any of these side effects occur, you must inform your study doctor immediately.

Side effects of T-DM1

Common side effects:

- Fatigue (tiredness)
- Nausea

- Bone and joint pain
- Muscle pain
- Low blood platelet count
- Headache
- Constipation
- Nerve damage
- Low red blood cell count
- Low potassium levels

Rare, serious side effects (occurring in 1-2% of patients):

- Heart problems (such as reduced heart function, congestive heart failure)
- Lung problems (such as inflammation of lungs with symptoms of trouble breathing, cough, tiredness, and fluid in the lungs)
- Liver problems (such as liver failure with symptoms of swelling/pain in the abdomen, yellow tint in the eyes/skin, swollen legs/feet/ankles)

Risk from Blood Collection

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Risks from Biopsy

Care will be taken to minimize risks that may happen during collection of a tumor sample. This procedure usually causes only brief discomfort at the site from which the biopsy is taken. You may experience some bruising around the biopsy site. Rarely, infection or bleeding may occur at the needle site.

Tumor biopsies will be done by a specialist using the CT scanner or ultrasound machine to guide the biopsy needle into the tumor to ensure accuracy. To collect the research biopsies as well as the biopsy that may be performed at screening, you may be exposed to up to 4 CT scans.

See Structural MRI

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. If you have a history of metastases to your brain or if we are concerned that you may have metastases to your brain, we will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner about 30 minutes. You may be asked to lie still for up to 30 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at anytime.

It is very important for the experiment that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.

We may place a bar in your mouth to help keep your head still.

Risks for MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Gadolinium enhanced MRI

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for research and medical purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The

effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

What are the risks of radiation from being in the study? below for more details.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control when starting study treatment, during study treatment, and for seven (7) months after you finish study treatment (the restricted period).

If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant while participating in this research study, please contact the study team as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. For males the restricted period is four (4) months. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

Two methods of birth control must be used. Acceptable birth control options for you and your partner include:

- Abstinence;
- hormonal contraceptives or therapies (such as birth control pills, injections, patch or implants);
- barrier methods (such as a condom, cap, or diaphragm) used with a spermicide;
- an intrauterine device (IUD), such as Copper T, Progesterone T, Levonorgestrel-releasing intrauterine system (e.g., Mirena);
- surgical sterilization (tubal ligation or vasectomy).

Men should refrain from donating sperm during the study and for 4 months after the last dose of study medications.

Structural MRI

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. If you have a history of metastases to your brain or if we are concerned that you may

have metastases to your brain, we will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner about 30 minutes. You may be asked to lie still for up to 30 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at anytime.

It is very important for the experiment that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.

We may place a bar in your mouth to help keep your head still.

Risks for MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Gadolinium enhanced MRI

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for research and medical purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives,

and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from CT scans and CT guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 11 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans and CT guided biopsies that you get in this study will expose you to the roughly the same amount of radiation as 36.7 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.1 out of 100 (1.1%) and of getting a fatal cancer is 0.6 out of 100 (0.6%).

You may not participate in this study if you are pregnant or breast feeding. If you are capable of becoming pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Non Radiation Risks of CT Scans

In addition to the radiation risks from CT scans discussed above, you may experience an allergic reaction to the dye we inject into your veins to help us view the scan better. You might experience

hives, itching, headache. More serious reactions that would include difficulty breathing, increased heart rate and swelling of your throat or other body parts.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefit to you might be stabilization or shrinkage of your tumor and a reduction in chances of developing new lesions with a decrease in symptoms caused by progressive disease.

Are there any potential benefits to others that might result from the study?

Despite advances in early detection and effective treatments, there is still a high incidence of invasive, metastatic breast cancer and therefore, there is a need for new beneficial treatments. In the future, other people might benefit from this study because of the knowledge gained from the outcome of this trial using a new combination immunotherapy.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with surgery, radiation or with drugs already approved by the FDA for your disease;
- choose to take part in a different study, if one is available; or
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

We do not plan to return research findings to you.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if she/he believes that it is in your best interest;
- if your disease worsens or comes back during treatment;
- if you have side effects from the treatment that your doctor thinks are too severe;
- if you become pregnant;

- if BN-Brachyury, Entinostat, M7824, and/or T-DM1 become unavailable;
- if new information shows that another treatment would be better for you;
- if you do not follow the study rules; and/or
- if the study is stopped for any reason.

In this case, you will be informed of the reason therapy is being stopped.

After therapy is stopped we would like to see you for a safety visit 28 days after your last dose.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Bavarian Nordic, Syndax, EMD Serono, Inc., or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your Specimens or Data be Saved for Use in Other Research Studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted future. These studies may provide additional information that will be helpful in understanding metastatic breast cancer or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will Your Specimens or Data Be Shared for Use in Other Research Studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your samples. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw the specimens and data.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

Will Your Genomic Data Be Shared Outside of This Study?

As part of this research, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH until they are no longer of scientific value or if you withdraw consent for their continued use, at which time they will be destroyed. Your specimens and data may be stored by the NIH indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your data or samples.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive compensation for participation in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will cover the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g. flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.

- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using:

- BN-Brachyury developed by Bavarian Nordic,
- Entinostat developed by Syndax, and
- M7824 developed by EMD Serono, Inc.

through a joint study with your study team and the company. The companies also provide financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Some of your health information, and/or information about your specimens, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Institutes of Health and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- The National Institutes of Health Intramural Institutional Review Board.
- The study Sponsor, Center for Cancer Research, or their agent(s).
- Qualified representatives from Bavarian Nordic, the pharmaceutical company who produces BN-Brachyury, or their agent(s).

- Qualified representatives from Syndax, the pharmaceutical company who produces Entinostat, or their agent(s).
- Qualified representatives from EMD Serono, Inc., the pharmaceutical company who produces M7824, or their agent(s).

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens and data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy

Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

Policy Regarding Research-Related Injuries

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

Problems or Questions

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Fatima Karzai, MD, fatima.karzai@nih.gov, 301-480-7174. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

Consent Document

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.