A Phase II Non-randomized Study to Assess the Safety and Efficacy of the Combination of Tucatinib and Trastuzumab and Capecitabine for Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer

NCT#: 03501979

Date: 7/28/2022

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM
(Part One: Ommaya reservoir)

TITLE: A phase 2 non-randomized study to assess the safety and efficacy of the combination of tucatinib and trastuzumab with capecitabine for treatment of leptomeningeal metastases in HER2-neu positive breast cancer

IRB PROTOCOL NO.: IRB-300000290

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SPONSOR: University of Alabama at Birmingham

SPONSOR PROTOCOL NO.: TBCRC 049

SUPPORT PROVIDED BY: MD Anderson Cancer Center; Seattle Genetics, Inc.; Johns Hopkins University on behalf of the Translational Breast Cancer Research Consortium (TBCRC)

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WHAT IS A CLINICAL STUDY?

A clinical study is a research study that tests the effects of a new medicine or treatment in people.

Your study doctor will explain the study to you. The study will only include people who understand the study, meet the study's entry criteria, and choose to be in it. If you choose to volunteer for this study, you will be asked to sign this form. This process is called informed consent.

This form explains what the study is about, how it will be done, the possible risks, benefits, and side effects of participating in the study and your responsibilities as a participant. This form will answer some questions about the study, but you should speak with your study doctor if you have additional questions. Please take your time to review the information in this form carefully. You may take home an unsigned copy of this form for review before making a decision.

If you have any questions about the study, or if this form has any words that you do not understand, ask your study doctor or the study staff. You may also want to talk to others (for example, your friends, family, or other doctors) about being in this study.

You do not have to be in this study. You are free to say 'yes' or 'no', or to drop out at any time. No penalty or loss of benefits will occur if you say 'no' or stop participating. Whatever—and whenever—you make your decision, your regular medical care will not be affected by your decision.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to evaluate a new treatment for patients with HER2+ Metastatic Breast Cancer (MBC) with leptomeningeal disease (LMD).

Currently, there is no standard of care for the treatment of metastatic HER2-neu positive (HER2+) metastatic breast cancer (MBC) with leptomeningeal disease (LMD). When breast cancer has spread to the meninges (tissues that surround the brain and/or spinal cord), LMD is diagnosed. LMD is a rare and fast growing form of cancer with few treatment options. Therefore, further study in search of new treatments is needed.
We want to find out what effects, good and bad, using a combination of tucatinib and trastuzumab with capecitabine has on patients with HER2+ MBC with LMD.

We think that this combination therapy will be safe and well-tolerated with few side effects and will control LMD and disease in the body. We also hope that this combination of drugs will improve survival with few side effects in patients diagnosed with metastatic breast cancer with LMD. As part of this study we will also collect samples, such as blood and spinal fluid, to assess the effects of the drug in the body and on the cancer, which may help us to understand why patients do and do not respond to therapy.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

We plan to enroll a total of 30 patients for the study across approximately 10 sites with each site enrolling up to 5 patients.

This study is being led by investigators at the University of Alabama Birmingham (UAB) and MD Anderson Cancer Center (MDACC). This study is being supported administratively and/or through funding by both UAB and MDACC, as well as by Seattle Genetics, Inc. and Johns Hopkins University on behalf of the Translational Breast Cancer Research Consortium (TBCRC). The TBCRC is a group of academic medical centers across the United States that work together to conduct breast cancer research.

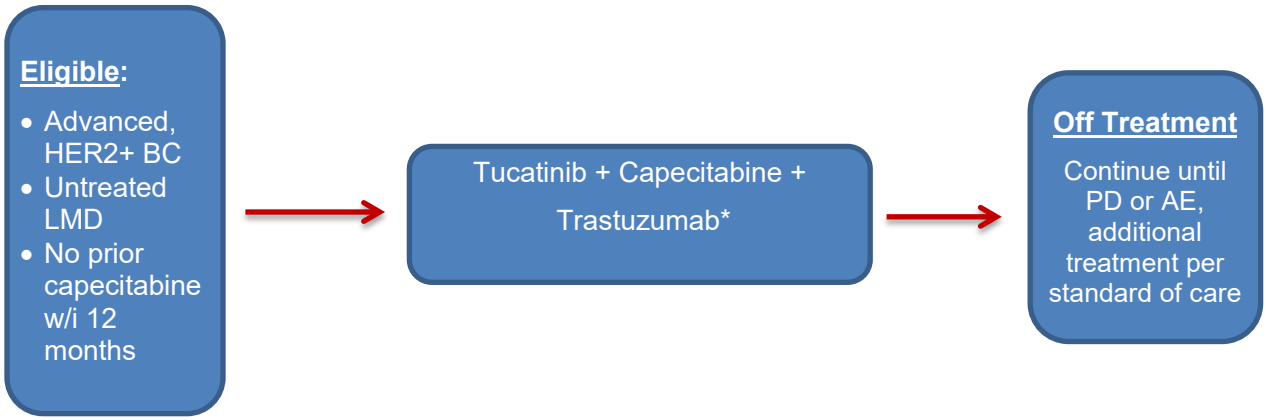
HOW IS THIS STUDY DESIGNED?

If you complete the consent process, then you may be eligible to participate in this study. Eligible participants will receive tucatinib, capecitabine, and trastuzumab.

The research team wants to learn:

- What effect tucatinib has (if any) when given with capecitabine and trastuzumab on the growth of tumors in the brain and meninges (tissues that surround the brain and/or spinal cord).

STUDY DESIGN



WHAT DRUGS WILL BE TESTED IN THIS STUDY?

The drugs involved in this study are tucatinib, capecitabine and trastuzumab (or its biosimilar: Ogivri, Herzuma ,Ontruzant ,Trazimera Kanjinti in lieu of trastuzumab by the treating physician and site's discretion . Tucatinib is an oral tablet, which will be taken by mouth twice each day. The doses are generally taken about 12 hours apart and should be taken about the same time each day. The pills may be taken with or without food. You will be instructed on the dose and number of pills to take by your treating physician. Capecitabine is also in the form of tablets which will be taken by mouth twice each day for the first 14 days of each 21-day treatment period (also known as a cycle). It must be taken with food (within 30 minutes of a meal) with water. Your doctor will determine the number of pills to take at each dose. Trastuzumab will be given as an infusion (through a vein in your arm) once every 21 days. The length of each infusion is 30-60 minutes. For the very first dose of trastuzumab on the study, the length of the infusion may be longer.

You will be asked to record each dose of tucatinib and capecitabine on a study drug diary. You should bring your diary and all bottles of tucatinib and capecitabine with you to each clinic visit.

Please see the study calendar below, which shows what you can expect at each of your study visits.

Parameter	Screening	Treatment Cycles								End of Study
		1	2	3	4	5	6	7	8**	
Demographics	X									
CLINICAL EVALUATIONS:										
History and Physical	X	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X	X
Height	X									
Vital signs and Weight	X	X	X	X	X	X	X	X	X	X
Neurologic Exam[2]	X	X	X	X	X	X	X	X	X	X
LABORATORY/OTHER EVALUATIONS:										
Complete Blood Count	X	X	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel	X	X	X	X	X	X	X	X	X	
Pregnancy Test (serum or urine)	X									
CSF Evaluation	X	X	X	X	X	X	X	X	X	X
LVEF (Echocardiogram or MUGA)	X									
RADIOLOGIC EVALUATIONS:										
Extra-CNS/Systemic Staging	X					X				X
CNS/Neuroaxis Imaging[7]	X			X		X		X		X
TREATMENT ADMINISTRATION:										
Tucatinib + Capecitabine + Trastuzumab		X	X	X	X	X	X	X	X	
CORRELATIVE STUDIES:										
PK Samples: Blood and CSF[9]		X	X							
Non-PK Samples: CSF		X	X	X	X	X	X	X	X	X
Non-PK Samples: Blood		X	X	X	X	X	X	X	X	X
Symptom/QOL Questionnaires		X	X	X	X	X	X	X	X	X

**The above study calendar reflects 8 cycles of treatment. However, patients who are benefiting/responding to therapy may continue on for additional cycles and would undergo the same test as noted above at every other cycle.

Screening Tests and Procedures:
As part of the study screening process, this consent form must be signed. The following tests and procedures will be done during screening to determine if you are eligible to participate in the study. It is possible that these tests may show that you can't take part in the study. If this happens, your doctor will discuss these reasons with you.

At Screening/Baseline – within 28 days before enrollment/starting treatment
After you sign this informed consent form, tests or procedures will be done to find out if you can be in the study. These include the following:

- Review of your current symptoms, medications, active medical problems, and your medical history
- Physical examination (performed by medical oncologist)
- Neurologic physical exam (performed by a neurologist/neuro-oncologist)
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- ECHO (echocardiogram) or MUGA (multiple gated acquisition) scan to measure how much blood your heart pumps out with each heartbeat
- Performance status (measurement of how well you can carry out daily activities)
- Blood draws for routine laboratory tests and cancer biomarker studies (approximately 4 tablespoons). A biomarker is a molecule or cell in your body that can be found in your blood, body fluid or tissue and a biomarker can be used to measure your health.
- Cerebral spinal fluid (CSF) standard evaluation – the study doctor will obtain a CSF sample to assess cell count, evidence of tumor in fluid, and cancer research biomarkers.
- Blood draw to test for Hepatitis B and Hepatitis C (approximately 2 teaspoons). If this test is positive you may be asked to have another test to confirm the first result
- Tumor assessment by CT scan or MRI that takes cross-sectional pictures (slices) of your body
- MRI of your brain and spine
- Pregnancy Test (blood or urine) – only for participants of childbearing potential.

Each cycle visit, Day 1
- History and physical exam (performed by medical oncologist)
- Neurologic physical exam (performed by a medical oncologist and/or neurologist/neuro-oncologist)
- Performance status
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- Blood tests – CBC with differential, ALT, AST, alkaline phosphatase, total bilirubin, BUN/creatinine.
- Treatment will be given
- CSF samples
- Routine blood samples
- Symptom Burden and Quality of Life (QOL) Questionnaires

During Cycles 1 and 2 only – Days 1-2

- Pharmacokinetic (PK) studies to examine study drug levels in blood and CSF

Every 2 cycles (42 days)

- MRI brain and spine

Every 4 cycles (84 days)

- CT chest/abdomen/pelvis (CAP) and bone scan or PET/CT

End of Study

- History and physical exam (performed by medical oncologist)
- Performance status
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- Neurologic physical exam (performed by a neuro-oncologist or neurologist)
- CSF standard evaluation
- MRI brain and spine
- Symptom Burden and Quality of Life (QOL) Questionnaires

Biospecimen samples

Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, CSF, etc. Most biospecimens contain DNA, which is the genetic code for each person. In this study, the planned biospecimen samples are blood and spinal fluid. As part of this study, we may collect DNA (genetic information) about you and these data will be used for research purposes.

If you would like to review the information for this study, ask the study team doctor for the ClinicalTrials.gov study registration number. Also, the results of the trial will be available on the Translational Breast Cancer Research Consortium website.

HOW LONG WILL I BE IN THIS STUDY?

The study is expected to last for 3 years. Clinical trial participants will receive treatment until disease progression or unacceptable toxicity or death.

Clinical trial participants will be followed every 6 weeks via telephone call and/or chart review for 6 months after leaving the study, or until death, whichever occurs first. Participants who discontinue the study for unacceptable side effects will be followed in the same method.
In the event that a participant does not continue her post-study care at the clinic, every attempt will be made to collect this post study follow up information either by direct contact or through communication with your outside physician(s).

WHO WILL BE ON MY PATIENT CARE TEAM DURING THE COURSE OF THE STUDY?

- Breast medical oncologist
  - Perform physical exam (may include neurologic exam)
  - Review blood tests
  - Review imaging studies
- Neurologist/neuro-oncologist
  - Perform neurologic physical exam
  - Review imaging studies
  - Review CSF studies
- Procedure list
  - Depending on the institution where you enroll, there may be a separate team who helps with collection of CSF from the ommaya reservoir.
- Study coordinator and/or research nurse
  - Follow-up
  - Coordinate blood tests, imaging studies, collection of research samples, and treatments.

Your breast medical oncologist and neurologist/neuro-oncologist will work together to determine if it is safe for you to proceed with the next cycle of treatment and to determine disease status and benefit from treatment. If and when you discontinue treatment, the study coordinator/research nurse will call you via telephone or review your chart to perform study-related follow up.

WHAT ARE THE RISKS OF PARTICIPATING IN THE STUDY?

Your condition may not improve and could even worsen if you take part in this study.

You may have side effects as a result of your participation in this study. A side effect is an unwanted or unintended problem that may be caused by taking a drug.

If you take tucatinib, capecitabine and trastuzumab certain side effects and discomforts may happen after you take tucatinib, capecitabine and trastuzumab. Tucatinib, capecitabine and trastuzumab may affect several organs (or parts) of your body including, but not limited to, effects on your cancer cells. Side effects that you may have during this study may be minor, life-threatening, or even cause your death sooner than would have been expected from your cancer. You may also have other side effects that doctors don't know about yet. Your study doctor and other medical staff will be performing the procedures to reduce any side effects that may occur; however, you may have unforeseen side effects. You will be monitored closely (with blood tests, physical exams, and heart scans) for any side effects and the study therapy will be stopped if serious side effects happen. You will be asked to report any side effects or changes in your health to your doctor, no matter how minor the changes may seem to you.

Taking other drugs (including alcohol, over-the-counter medications, prescriptions, illegal drugs, herbal preparations, or nutritional supplements) may cause additional side effects or even life-threatening reactions when combined with the drugs or experimental agents used in this study. It is very important that you discuss ALL medications that you are taking with your study doctor.

RISKS ASSOCIATED WITH TUCATINIB

The most common side effects reported in patients with cancer treated with tucatinib include:

- Feeling sick to your stomach (nausea)
- Watery poop (diarrhea)
- Feeling tired (fatigue)
- Throwing up (vomiting)
- Rash
- Difficulty pooping (constipation)
- Cough
- Pain in your arms or legs (pain in the extremity)
- Back pain
- Headache
- Infection that could cause frequent and painful urination (urinary tract infection)
- Muscle pain (myalgia)
- Muscle and bone pain in your chest (musculoskeletal chest pain)
- Belly pain (abdominal pain)
- High levels of liver enzymes (increased liver function tests). This may mean you have a problem with your liver.
- Not wanting to eat (anorexia)
- Feeling dizzy (dizziness)
- Feeling out of breath (dyspnea)
- Patchy redness on your skin (erythema)
- Low levels of magnesium in your blood (hypomagnesemia). You may feel weak, have an abnormal heartbeat, muscle cramps, or seizures.
- Heavy sweating while sleeping (night sweats)
- Infection in the nose, sinuses or throat (upper respiratory tract infection). You may have fever, pain, or a hard time breathing.

Liver Function Problems

Some patients who took tucatinib had problems with their liver. Your doctor will run tests to check that your liver is working properly during your treatment with tucatinib. Your doctor may change your tucatinib dose based on the test results.

Diarrhea

Tucatinib can cause severe watery poop (diarrhea). If you have watery poop, tell your doctor **right away**. Your doctor may change your tucatinib dose if you have watery poop.

Kidney Function Problems
Some patients who got tucatinib had higher creatinine levels. This could mean that there are problems with your kidneys. If this happens, it's usually within the first treatment cycle. Patients who have had increased levels of creatinine had these levels stay increased while they were getting treated. The levels went back down after treatment stopped.

Other Important Side Effects

Interactions with Other Medications
Tucatinib may change how your body reacts to some other drugs, which could stay in your body longer than usual. While you are taking part in this study, you might need to stop some medications or replace them with other medications. If you can't stop taking these medications, your doctor might need to change how much you take. Your doctor might also need to watch your health more closely while you are taking part in this study.

Fertility, Pregnancy, and Breastfeeding Risks
Tucatinib could hurt or kill a baby developing in the womb. You should not try to get pregnant or get your partner pregnant while you are in this clinical trial or for 30 days after your last dose of tucatinib.

If you are pregnant or breastfeeding, you can't be in this study. We will remove anyone who becomes pregnant while on study from the study treatment immediately.

Tucatinib could hurt a breastfeeding baby. You must not breastfeed during the study or for 30 days after you stop treatment with tucatinib.

Tell your study doctor **right away** if

- you or your partner become pregnant while you are in this study
- you think that you are pregnant while taking part in this study
- you or your partner become pregnant within 30 days after being treated with Tucatinib.

Seattle Genetics would like to follow any pregnancy that happens during this study during the pregnancy and for some time after the birth of any child. If you give permission, we will follow your baby for up to 8 weeks after birth, or longer if there are problems. If your partner becomes pregnant, we will ask for their consent to follow their pregnancy and the health of the baby.

RISKS ASSOCIATED WITH CAPECITABINE

The most common side effects associated with capecitabine include:

- Nausea
- Diarrhea
- Abdominal pain
- Tiredness

- Acid reflux
- Eye tearing
- Fatigue (tiredness)
- Changes in taste
- Mouth sores
- Hair thinning
- Hand-foot syndrome (rash or skin changes on the hands and feet)
- Peripheral neuropathy (numbness and tingling in fingers and toes)
- Low blood counts
- Hyperbilirubinemia (abnormal liver function)

Management of capecitabine side effects may include temporary interruption, dose reduction, or treatment discontinuation with capecitabine.

RISKS ASSOCIATED WITH TRASTUZUMAB

Trastuzumab has different side effects that your study doctor will discuss with you. The most common side effects are:

- Allergic reaction to infusion
- Nausea/vomiting
- Tiredness
- Fever/chills
- Swelling of the legs and arms
- Anemia (low red cell count)
- Neutropenia (low white blood count)
- Congestive heart failure (damage to heart)

Note: Management of left ventricular dysfunction (heart failure), or infusion reactions may include temporary interruption or stopping treatment of trastuzumab permanently.

RISKS OF DRAWING BLOOD:

Drawing blood may cause pain, bruising, lightheadedness, and on rare occasions, infection.

MANDATORY OMMAYA RESERVOIR PLACMENT

All patients enrolled on the first stage of the study, MUST undergo MANDATORY placement of an ommaya reservoir if you do not already have one in place. An Ommaya reservoir is a small drum-like device that is placed under the skin of the skull to give chemotherapy and/or medicines. Placement of an Ommaya reservoir is usually recommended as standard of care in patients with newly diagnosed leptomeningeal disease and will be covered by your insurance. Although the reservoir is not being used to deliver chemotherapy to the brain in this study, it will be useful to assess your response to

treatment, as determined by your doctor. If you have one and/or have one placed, it will also be used to collect the study-required CSF samples rather than needing to undergo repeated lumbar punctures. To collect samples from the reservoir, it works similar to a port in that it is tapped or accessed with a needle to remove or collect CSF fluid. This fluid is then sent to the lab to detect any abnormal cells or collected for the research study. The risks of drawing CSF fluid are also as noted above. Your doctor can explain the standard of care ommaya reservoir placement procedure and discuss the risks with you.

How is the Ommaya reservoir is placed?

An Ommaya reservoir is implanted by a brain surgeon while you're under general anesthesia.

Preparation:

Getting an Ommaya reservoir implanted does require some preparation, such as:

- Not drinking alcohol once the procedure is scheduled
- Not taking vitamin E supplements within 10 days of the procedure
- Not taking aspirin or medications containing aspirin during the week before the procedure
- Telling your doctor about any additional medications or herbal supplements you take
- Following your doctor's guidelines about eating and drinking before the procedure

Recovery

Once the Ommaya reservoir is placed, you'll feel a small bump on your head where the reservoir is. You'll likely need a CT scan or an MRI scan within a day of your surgery to make sure it's correctly placed. If it needs to be adjusted, you may need a second procedure.

While you recover, keep the area around the incision dry and clean until your staples or stitches are removed. Be sure to tell your doctor about any signs of infection, such as:

- Fever
- Headaches
- Redness or tenderness near the incision site
- Oozing near the incision site
- Vomiting
- Neck stiffness
- Fatigue

Once you have healed from the procedure, you can return to all of your normal activities. Ommaya reservoirs don't require any care or maintenance.

Is it safe?

Ommaya reservoirs are generally safe. However, the procedure to place them carries the same risks as any other surgery involving your brain, including:

- Infection
- Bleeding into your brain
- Partial loss of brain function

To prevent infection, your doctor might prescribe you antibiotics following the procedure. Talk to your doctor about any concerns you have about complications. They can go over their approach with you and let you know about any additional steps they'll take to lower your risk of having complications.

Can it be removed?
Ommaya reservoirs usually aren't removed unless they cause problems, such as an infection. Though at some point in the future you may no longer need your Ommaya reservoir, the process to remove it carries the same risks as the process to implant it. Generally, removing it isn't worth the risk.

If you have an Ommaya reservoir and are considering having it removed, make sure you go over the potential risks with your doctor.

RISK OF DRAWING CSF FROM OMMAYA RESERVOIR

- Pain
- Bleeding
- Infection
- Headache
- Nausea/Vomiting
- Others as explained to me by my doctor

    - **Note:** This procedure is required for the first stage or the first 15 patients to enroll on the study so that your CSF can be collected for standard evaluation and to study drug levels in the fluid. If you are enrolling in the study on the 2nd stage, it is strongly recommended that you have an ommaya reservoir placed to help with collection of your CSF during the study for standard evaluations, which help determine if you are responding to the treatment. Alternatively, this can be done via lumbar puncture. Your study doctor will clearly discuss the stage of the study in which you will be enrolled.

RISK OF DRAWING CSF FROM OMMAYA RESERVOIR OR VIA LUMBAR PUNCTURE:

- Pain
- Bleeding
- Infection
- Headache
- Nausea/Vomiting
- Others as explained to you during the procedure

RADIATION RISKS ASSOCIATED WITH SCANS AND X-RAYS:

While you are in this research study, CT scans, PET/CT scans, bone scans, x-rays, and/or other radioactive agents may be used to evaluate your disease status. The frequency of these exams is similar to that which you would receive as standard care. There is thought to be a small but increased risk of cancers associated with radiation in the long term over many years.

Risks Associated with CT Scans:

In this study, you will be exposed to some radiation from the CT scan[s]. The total radiation from each [combined chest, abdominal and pelvic] CT scan is approximately equal to [five years] of exposure to natural background radiation. Background radiation is radiation normally received from sources such as cosmic rays and natural radioactivity in building materials and the ground. There is a small risk that the radiation may cause cancer or other radiation effects in several years.

To prepare you for your CT scan, a liquid called a "contrast dye" may be injected into your veins to improve the quality of the image. There is a small possibility that you could have a severe allergic reaction to this dye that could cause injury or death. If you have any kidney problems, the dye may cause other medical problems.

• If you have any kidney problems or have ever had an allergic reaction to contrast dye, you must let the study physician know as soon as possible.

RISKS ASSOCIATED WITH MRI SCANS:

When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your doctor. Your doctor may give you a medication to make you feel more comfortable in a confined space. A magnetic resonance imaging (MRI) exam is a test that uses magnetic fields and radio waves to generate images of the inside of your body. You will be placed inside a scanner and asked to lie still for approximately 30 minutes. This is a noisy exam; you will be given earplugs to protect your hearing. During the scan, a liquid will be injected into your vein to

improve the quality of the scan.

MRI has negligible risks for most people; however, if you have any metal objects in your body MRI may not be safe for you and you will not be allowed to take part in this study.

RISKS ASSOCIATED WITH MRI SCANS WITH GADOLINIUM AS A CONTRAST AGENT:

A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time), low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than on in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.
Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic sclerosing fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

REPRODUCTIVE RISKS:

We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus. Administration of the drug resulted in harm to the fetus of pregnant animals and could cause harm or death to a baby developing in the womb. Women who can become pregnant must take a pregnancy test before the start of the study.
While participating in this research study, you should not become pregnant or father a child, and should not nurse a baby as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex.

You must agree to use an adequate method of birth control during the study (such as surgical sterilization, IUDs or abstinence). Barrier methods such as diaphragms or condoms may also be used if a spermicide is used with them. Women cannot use birth control pills due to effects that they cause on breast cancer.

If you think you may be pregnant (have a missed or late menstrual period) at any time during this study, you must let the study doctor know immediately. Women who become pregnant will be removed from the study. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

Birth Control Requirements

If you can get pregnant, you must use a safe birth control method while you are taking part in this study. Safe birth control methods fail less than 1% of the time. This means that if 100 people used this birth control for a whole year, at most 1 person would get pregnant. You must use safe birth control methods while you take part in the study and keep using them for 30 days after stopping all study treatment. If you don't use safe birth control methods while you take part in the study, we might decide that you can't take part in the study anymore.
The safe birth control methods that you can use are:

- hormonal methods that have both estrogen and progestogen. These can be taken by mouth (birth control pills), inserted into the vagina, or absorbed through the skin (patches).
  hormonal methods that have only progestogen. These can be taken by mouth (birth control pills), injected, or implanted in your body.
- intrauterine device (IUD)
- intrauterine hormone-releasing system
- tubal ligation for females ("tubes tied")
- vasectomy for males

Talk with your doctor about your birth control options. You may also choose to not be sexually active (complete abstinence) while you take part in the study.

If you are able to get someone pregnant, and your partner is able to get pregnant, you must use a barrier method such as a male or female condom when you are taking part in the study. You must keep using a barrier method for 30 days after finishing treatment with tucatinib.

If you think you may be pregnant (have a missed or late menstrual period) at any time during this study, you must let the study doctor know immediately. Women who become pregnant will be removed from the study. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

Fertility Risks
It is not known if patients in this trial will have problems getting pregnant after taking tucatinib.

DRUG INTERACTIONS:

The other medications you take may affect the study drug(s) in ways that we do not know. For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter (OTC) drugs, vitamins, and natural remedies that you are taking before you start the study and before taking any of these products while you are on the study. Please be sure to tell us also about any changes you make with your medications during your participation.

QUESTIONNAIRES:

The research study questionnaires ask about quality of life, including emotional issues. On average, they are expected to take you approximately 30 minutes to complete. Answering some of these questions may cause discomfort. You may choose not to answer one or any of the questions on the questionnaires. If you choose not to answer any questions, it will not negatively affect your status as a participant. If one of the questionnaires that you are asked to fill out upsets you, please tell the research assistant who gave you the forms to fill out.

NON-PHYSICAL RISKS:

Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

During the research study, you will be provided with any new information that may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

RISKS ASSOCIATED WITH GENOMIC TESTING

Despite the GINA protections and the best efforts of the research team, there may still be a risk if information about you were to become known to people outside of this study.

Genetic information is unique to you, even without your name or other identifiers. For this reason, genetic information like DNA may be used to identify you and possibly your family members. We have procedures (such as, labeling your biospecimens with a password protected code known only to select research staff) to prevent people working with your DNA from discovering if it belongs to you. However, there is the risk this can happen as new ways of tracing genetic information are being developed that may make re-identification of genetic information possible.

BENEFITS

Taking part in this research study may or may not make your health better. We hope the information learned from this research study will help doctors learn more about the combination of tucatinib and trastuzumab with capecitabine as a treatment for breast cancer in the future. We hope the information learned from this research study will help breast cancer patients in the future.

ALTERNATIVES

There are other options to treat metastatic HER2 positive breast cancer with leptomeningeal disease that may include radiation, chemotherapy injected through the spinal canal, or chemotherapy given intravenously. Your doctor will discuss these other options with you.

SIGNIFICANT NEW FINDINGS

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

CONFIDENTIALITY

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of MD Anderson Cancer Center, Seattle Genetics, Inc., and Johns Hopkins University on behalf of the TBCRC; the Office for Human Research Protections (OHRP) and FDA. The information from the research may be published for scientific purposes; however, your identity will not be given out. This consent document will be placed in your file at UAB and the document will become part of your medical record chart.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System

affiliated entities so that the costs for clinical services can be appropriately paid for by either the study account or by the patient/patient's insurance.

Your medical record may indicate that you are on a clinical trial and will provide the name and contact information for the principal investigator.

Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

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.

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

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

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study without your consent if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

WHAT ARE MY COSTS FOR PARTICIPATING IN THIS STUDY?

If you participate in this study, there may be additional costs to you. Participation in this study is not a substitute for health insurance. You, or your insurance company, will be responsible for paying for standard of care expenses associated with your cancer. Standard of care expenses are routine treatment costs you would have incurred even if you were not in the study (such as blood tests, X-rays, CT or MRI scans, or physician's charges) and those used to manage or treat side effects of your cancer (such as transfusions, anti-nausea drugs, etc.). For this study, capecitabine and trastuzumab are also considered standard of care. Your insurance company may not pay for the standard of care costs when they are associated with studies like this one. You will be responsible for all of the costs linked with this study that are related to standard of care and not covered by other payers (HMO, health insurance company, etc.). You will be responsible for any co-payments or deductibles required by your insurance company.

The study will pay for the following items while you participate in this study:

- Tucatinib
- Any study-related procedures which are required solely for this study and which are not considered standard of care

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

If you take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from your medical team.

By signing this form, you do not waive any of your legal rights to seek payment in the case of injuries resulting from this study.

The treating institution will receive direct and indirect payment from Seattle Genetics, Inc. and Johns Hopkins University on behalf of the TBCRC (the study supporters) for their time spent doing research and general administrative services for this study. Seattle Genetics, Inc., and other company(ies) involved in the research studies done on blood and tissue samples may benefit financially from this research. You will receive no financial benefit from this research.

If you decide to sign this consent form, you are giving your bodily fluids and tissue samples collected during the study and any new drugs that may be developed from your fluids or samples.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

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

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

Side effects or harm are possible in any research study, and you might be injured or develop medical complications because you take part in this study. Medical complications could occur through no fault of yours or the study doctors involved. Known side effects have been described in this consent form, and there may also be unexpected side effects. It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study.

In the event you have an injury, the treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury.

Your health insurance company may or may not pay for treatment of injuries as a result of your taking part in this study. You should consult with your insurance company if you have questions. Additional reimbursement or compensation for study-related injuries (such as payments for costs like lost wages, or for pain and suffering, or for expenses other than medical care) are not provided.

You do not give up any of your legal rights to seek payment for study-related injuries by signing this form or by agreeing to participate in this study.

HOW WILL I BE INFORMED OF TRIAL RESULTS?

You will not be informed of the trial results. After the trial is completed, a summary of the results will be posted on the TBCRC (Translational breast cancer consortium) website. Additionally, you may visit clinicaltrials.gov and look up the trial with the NCI trial number. This can be provided to you from your medical team.

WILL I HAVE ACCESS TO THE STUDY DRUGS AFTER THE TRIAL IS OVER?

You will have access to the treatment until the time of disease progression, death, or unacceptable toxicity. However, it is possible that the trial may be discontinued early by the sponsor and research team if the combination is found to be unsafe or if it is determined to not be working well.

The trial may be stopped after the first 15 patients are enrolled if there are fewer than 2 patients with response to study therapy in the leptomeningeal disease. In the event, the trial is stopped for this reason, you will be allowed to continue on study as long as the treatment is continuing to benefit you; however, no additional patients will be allowed to enroll on the study.

QUESTIONS

If you have any questions, concerns, or complaints about the research or a research- related injury including available treatments, you may contact Dr. Erica Stringer-Reasor. She will be glad to answer any of your questions. Dr. Stringer-Reasor's number is 205-975-2816. She may also be reached after hours by paging at 205-934-3411.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

WHAT ARE MY LEGAL RIGHTS?

You are not waiving any of your legal rights by signing this informed consent document.

BIOSPECIMENS FOR RESEARCH

Your bio-specimens (tissue and blood samples) are being used for this research study. As part of the study, we may perform the following research studies on them. In addition, we will ask your permission in the next section for the use of any leftover bio-specimens (that is, samples remaining or "leftover" after the research for this study is completed) to be used for future research and the option to contact you in the future.

We may use genetic analysis in some of the research we do on your samples. Researchers can learn a lot by studying genes. Genes are pieces of DNA that give instructions for building the proteins that make our bodies work. DNA stores these instructions in the form of a code. This is the code that you inherit from your parents and that you pass on to your children.

One of the methods we might use to study your samples is called whole genome sequencing. This allows us to look at some or all of your genetic code. Researchers may also use other methods as they are developed. Studying genes along with your health information will help us to better understand

what causes certain diseases. It may also help us to understand how different patients respond to treatment. This knowledge could help us to develop treatments for everyone.

What we learn about you from your samples will not be put in your health record and will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results. Your samples will only be used for research and will not be sold. Health insurance companies and group health plans may not request your genetic information that comes from this research.

We will remove your name and any other information that could directly identify you from your samples and information. We will replace this information with codes. We will keep a master list that links those codes to your materials. Only certain study staff can access this master list. We will keep the samples in locked freezers in locked buildings. We will keep health information and research data on secure computers. These computers have many levels of protection.

The Genetic Information Nondiscrimination Act (GINA) may help protect you from health insurance or health-related employment discrimination based on genetic information. The law provides that health insurance companies and group health plans:

- May not ask for genetic information from this research and
- May not use genetic information when making decision about eligibility or premiums

The law will not stop health insurance companies from using genetic information to decide whether to pay claims. The law does not apply to other types of insurance (such as life, disability or long-term care).

Despite the GINA protections and the best efforts of the research team to protect your information, you may still be at risk if information about you were to become known to people outside of this study.

Q. WHAT ABOUT USE OF MY TISSUE AND BLOOD FOR FUTURE RESEARCH? - OPTIONAL

If part of the tissue from the required biopsies or blood from the required draws in this study as described above is leftover after the proposed tests are done, we ask you to donate those left over samples for future research. If you do not want to take part in this optional portion of this study, you may still take part in the main study as described above.

If you agree, your samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples.

What research will be done on my leftover samples and what information will be collected?
The future research may also include looking at genes (DNA) and how they affect health and disease. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

In addition to your samples we will store some basic information about you. This will include things like age, sex, and race or ethnic group. We will store information about your family's health history. If you agree, we will collect this information from your medical record.

We will also collect information from your medical record that is related to your health and/or disease history. Some examples include results of tests, medical procedures, images (such as X-rays), and medicines you take. Researchers will use this information to better understand how genes affect health and response to treatment. We will look at your medical record from time to time to update this information. This will take place for as long as your sample is stored, which may be many years, unless you tell us to stop.

Who will have access to my leftover samples and information?
We will store your samples and information in a tissue bank. Your samples will be coded similarly as described previously.

Researchers can ask to study the materials stored in the tissue bank. This includes researchers from within the TBCRC Institutions, as well as from other universities, the government, and drug or health companies. Some researchers will be from the U.S.; some may be from other countries around the world. An oversight committee will review each request.
This kind of review is to make sure that any risks are minimized and that your rights and welfare are protected. If a study is approved, we might give a part of your sample and information to the researchers. We would give them your materials along with samples and information from many other people. We may also share your materials with other tissue bank and research projects. We will not share information that could directly identify you (like your name, social security number, and address) without your permission.

There is no limit on the length of time we will store your samples and information. We may keep using them for research indefinitely unless you decide to withdraw from the project.

Who else will have access to my genetic information?
Researchers can do more powerful studies when they share with each other the information they get from studying human samples. They share this information with each other by putting it into scientific databases. These databases store information from many studies conducted in many different places. Researchers can then study the combined information to learn even more about health and many different diseases.

There are different kinds of databases; some are publicly accessible and some are restricted. Anyone on the Internet can access publicly accessible databases. Only researchers who apply and are approved can access restricted databases. There are many restricted databases; the researchers in this study maintain some, the federal government maintains some, and private companies maintain some. Some of your genetic and health information could be placed into one or more of these publicly accessible or restricted databases.

Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database.

However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is very small, but may grow in the future. Researchers will always have a duty to protect your privacy and to keep your information confidential.

Will I find out the results of the research?

You should not expect to get personal results from research done through the tissue bank. Researchers will study samples and information from many people and it may take many years before they know the results or if they have any meaning. However, it is possible that researchers will learn something that might be important to your health, such as results of genetic or similar testing done on your samples. We expect these situations to be very rare. If this happens, we will seek appropriate approvals from the IRB and/or ethics committee and may contact you directly or through your doctor to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted. The findings may lead to additional testing or changes to your care, and could be a stressful situation to you and your family. If this happens, care will be taken to make sure the findings are carefully explained and that support is available for you.

Will this future research cost me anything or will I be paid?

You will not be asked to pay any costs related to this research. You will not be paid for agreeing to allow your samples to be used for future research.

The research done with your tissue and blood may lead to the development of new products in the future. You will not own any product or idea created by the researchers working on blood or tissue obtained from you during this study. You will not receive any financial benefit from the creation, use or sale of such a product or idea from blood or tissue obtained from you during this study.

Your tissue and blood will be used only for research and will not be sold.

What are the risks?

One risk of giving samples for this research may be the accidental release of your name that could link you to the stored samples and/or the release of results of the tests run on your samples, including genetic testing. There are safeguards in place such as coding your samples and information, secure buildings and equipment, and the Genetic Information Nondiscrimination Act (GINA) as described previously.

What are the benefits?

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Will I be contacted in the future about this or other research?

We, the local site Study Team, may want to contact you in the future. You can decide now whether or not you want to be contacted. You can also change your mind later.

If you agree, we may contact you for several reasons. For example, over time, stored samples may be used up or decrease in quality, so we may contact you to ask for more samples. We may also contact you to update basic information or request information about your health.

Additionally, we may want to contact you to see if you want to participate in other research. We will not notify you every time your samples and information are used. However, some researchers might apply to do a study for which they would need to contact you. For example, they might want to ask you to give another sample or to fill out a survey, or they might ask you to do a phone interview or come in to be seen by a researcher or doctor. If a study like this is approved, someone from this project will contact you. They will tell you about the study so you can decide if you want to receive more information. There will be a new consent process just for that study. You can decide then to take part or not take part. If at any time you decide you no longer want to be contacted about future studies, please tell us.

Can I change my mind after I agree to let my samples be used?
You have the right change your mind about the future use of your leftover bio-specimens and information at any time. If you want to leave the project, let us know. You will be given some options and can choose what you want us to do with your unused samples. You can also tell us to stop using your medical records. However, you cannot withdraw your samples and information from studies that have already begun. We cannot get samples and information back once they are shared with other researchers. In addition, it may not be possible to remove your genetic information from scientific databases once it has been de-identified.

MAKING YOUR DECISION
You have a say in how your leftover bio-specimens and information are used in future research. Donating samples for future research is your choice and you may be in the study even if you do not want your samples used or stored for future research.

Please review each question below and choose the answer that is best for you:

1. I permit leftover samples to be stored and used for future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. I permit my samples to be stored and used for future research about other health problems (for example: causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. I agree that someone may contact me in the future to ask me to take part in more research.

☐ Yes ☐ No Please initial here: _____ Date: _____

4. I agree to have my coded genetic information and coded medical information placed in password-protected secured databases for research analyses.

☐ Yes ☐ No Please initial here: _____ Date: _____

SIGNATURES

Your signature below indicates you agree to participate in this study. You will receive a copy of this signed consent form.

_____

Signature of Participant Date

_____

Signature of Person Obtaining Informed Consent Date

University of Alabama at Birmingham

AUTHORIZATION FOR USE/DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol: **A phase 2 non-randomized study to assess the safety and efficacy of the combination of tucatinib and trastuzumab with capecitabine for treatment of leptomeningeal metastases in HER2-neu positive breast cancer**

UAB IRB Protocol Number: **IRB-300000290**
Principal Investigator: **Erica Stringer-Reasor, M.D.**
Sponsor: **University of Alabama at Birmingham**

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research, and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, MD Anderson Cancer Center, Seattle Genetics Inc., Johns Hopkins University on behalf of the Translational Breast Cancer Research Consortium (TBCRC), providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____