COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

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

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Study Title: HER2CLIMB (ONT-380-206): Phase 2 Randomized, Double-Blinded, Controlled Study of ONT-380 vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma

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Funding Source: Cascadian Therapeutics, Inc.

Invitation to Participate and Description of Project

You are invited to take part in a research study. The research study is designed to test the combination of an investigational drug (ONT-380) with two approved drugs (capecitabine and trastuzumab) in people with advanced breast cancer to find out what effects, good or bad, it may have on you and your disease. You have been invited to take part because you have advanced breast cancer for which capecitabine and trastuzumab are standard treatments.

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

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

The research study is being sponsored by Cascadian Therapeutics, Incorporated (Inc.). Cascadian Therapeutics, Inc. is called the Sponsor and Yale University is being paid by Cascadian Therapeutics, Inc. to conduct this research study. Dr. Michael DiGiovanna is the principal investigator of this study at Yale Cancer Center.

Purpose

The purpose of this study is to test the combination of an investigational drug (ONT-380) with two approved drugs (capecitabine and trastuzumab) in people with advanced breast cancer to find out what effects, good or bad, it may have on you and your disease.

The study drug that will be used in this research study, ONT-380, is investigational. This means it has not been approved for commercial use by the United States Food and Drug Administration (FDA). Capecitabine and trastuzumab are approved by the Food and Drug Administration (FDA) and are used either together or in combination with other drugs as part of the standard of care for patients who have metastatic breast cancer that is HER2+ (positive). HER2 stands for Human Epidermal growth factor Receptor 2. HER2 receptors are found on the surface of cells in the body. HER2 receptors help send messages that tell the cell to grow and divide. In HER2+ cancers, the cancer cells have an abnormally high number of HER2 receptors. HER2+ tumors tend to grow and spread more quickly than tumors that are not HER2+.

This is the second study of the combination of ONT-380, capecitabine and trastuzumab, and this is the fifth study of ONT-380 tested in subjects with advanced breast cancer.

It is expected that 180 subjects will participate in this study at 90 sites in North America and 19 sites in Western Europe. It is expected that approximately 14 subjects will be enrolled at Yale Cancer Center.

Study Procedures

If you complete the consent process then you may be eligible to participate in this study.

If you are eligible to participate, you will be "randomized" into one of two study groups: One group will receive ONT-380, capecitabine and trastuzumab. The other group will receive a placebo (a placebo is something that looks like medicine but is not actually medicine), capecitabine and trastuzumab. Twice as many subjects will be assigned to the ONT-380 group as will be assigned to the placebo.

Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor the researchers will choose or know the group to which you are randomized. Once you have been assigned to a group your group cannot be changed.

The sponsor and study doctors want to learn:

- What the side effects of ONT-380 are when given with a standard dose of capecitabine and trastuzumab (good and bad)
- What effect ONT-380 has (if any) when given with a standard dose of capecitabine and trastuzumab on the growth of tumors outside of the brain when compared to placebo
- What effect ONT-380 has (if any) when given with a standard dose of capecitabine and trastuzumab on the growth of tumors in the brain

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

All of the computed tomography (CT) and magnetic resonance imaging (MRI) images taken during the study will be sent to a central radiologist, chosen by the sponsor, for an independent second review. You will not be identified in these scans. The results of the independent review will not be reported to you or your doctor and will not be used to make any decisions about your clinical care.

Screening Period

If you agree to participate and sign and date this form*, you will need to undergo a series of tests and procedures to determine if you are eligible to participate in the research study. You will come to the study site for screening tests and it is possible that more than one screening visit may be needed. Screening tests can be done up to 28 days before the first dose of ONT-380/placebo, capecitabine and trastuzumab and include:

- Review of your current symptoms, medications*, active medical problems*, and your medical history
- You may be asked to allow a portion of a previous tumor tissue to be retested or to have a new biopsy (the removal of tissue from your tumor using a needle) to confirm your tumor cells contain HER2* (if not already done during pre-screening, prior to signing this consent)
- Physical examination
- 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 (such as blood sugar, kidney and liver function tests, among other tests) and cancer biomarker studies* (approximately 4 tablespoons)
- 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*

- Blood draw for pregnancy test of approximately 1 teaspoon (not required for females of non-child-bearing potential or males). This test must be done *within 7 days* of the first dose of ONT-380 /placebo, capecitabine and trastuzumab*
- Urine sample for urinalysis*
- Tumor assessment by CT scan or MRI that takes cross-sectional pictures (slices) of your body
- MRI of your brain*
- Electrocardiogram (ECG) to check the electrical activity of your heart*

Treatment Period
The drugs involved in this study are ONT-380/placebo, capecitabine and trastuzumab. ONT-380 and the placebo are in the form of tablets which will be taken by mouth twice each day. 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 cycle. Trastuzumab will be given as an infusion (through a vein in your arm) once every 21 days. In certain situations, your doctor may give you trastuzumab more than once every 21 days and will discuss that with you if it applies to you.

Your responsibilities in this study are:

- Keep all your appointments, have all of the study tests and procedures, and follow all instructions given by the study doctor or staff
- Keep the study doctor informed of any new medications you begin taking after signing this consent form (including, over-the-counter, prescription, illegal, herbal preparation, or nutritional supplement)
- Tell the study doctor about any change in how you are feeling, and be sure to tell them about any problems or side effects that you experience while you are in the study
- Do not become pregnant or get your partner pregnant during the study or for 6 months after your last dose of the study drug combination you are assigned to receive. If you become pregnant or father a child, immediately tell your doctor if either of these events occur during the study

Monitoring Tests and Procedures:
During the study, to find out how you are doing, the following tests and procedures will be performed, physical exams will be given, and you will be interviewed by medical staff at the hospital. Visits occur in “cycles” and a cycle happens about every 21 days. Unless otherwise specified below all ONT-380/placebo and capecitabine doses may be taken at home.

Monitoring tests and procedures include:

Cycle 1 Day 1 (clinic visit)
- You will be asked if you have any side effects or new medical problems and what they are*
- You will be asked about all medications you are currently taking*

- Physical examination[+]
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- Performance status (measurement of how well you can carry out daily activities)[+]
- Blood draws for routine laboratory tests (approximately 3 teaspoons)[+]
- You will take the morning dose of ONT-380/placebo in the clinic (and the evening dose on your own at home)*
- You will take the morning dose of capecitabine in the clinic (and the evening dose on your own at home)
- You will be given an infusion of trastuzumab into a vein in your arm

[+]These procedures may not need to be repeated if they have been done within 96 hours of your visit during the screening process

Cycle 1 Day 12 (clinic visit)

- You will be asked if you have any side effects or new medical problems and what they are*
- You will be asked about all medications you are currently taking*
- Physical examination
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- Performance status (measurement of how well you can carry out daily activities)*
- Blood draws for routine laboratory tests (approximately 3 teaspoons)

Cycle 2 Day 1 (clinic visit) and Day 1 of All Later Cycles

- You will be asked if you have any side effects or new medical problems and what they are*
- You will be asked about all medications you are currently taking*
- Physical examination
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- Electrocardiogram (ECG) to check the electrical activity of your heart during cycles 2-4 only*
- Performance status (measurement of how well you can carry out daily activities)
- Blood draws for routine laboratory tests (approximately 3 teaspoons)
- Blood will be drawn prior to receiving ONT-380/placebo to look at the levels of ONT-380 in your blood (during cycles 2-6 only and approximately 1 teaspoon each time)*
- Blood will be drawn 1-4 hours after receiving ONT-380/placebo to look at the levels of ONT-380 in your blood (during cycle 3 only and approximately 1 teaspoon)*
- Urine pregnancy test every three cycles starting at cycle 3 (not required for females of non-child-bearing potential or males). If the urine test is positive a blood test to confirm the result will be required*
- You will take the morning dose of ONT-380/placebo in the clinic (and the evening dose on your own at home) during cycles 2-6 only. After cycle 6 you can take both the morning and the evening dose at home*

- You will be given an infusion of trastuzumab into a vein in your arm

Cycle 2 Day 12 (clinic visit)

- Blood draws to check your liver (approximately 1 teaspoon)

Every six weeks starting from Cycle 1 Day 1 through week 24 and every nine weeks thereafter through end of treatment (clinic visit)

- Tumor assessment by CT scan or MRI that takes cross-sectional pictures (slices) of your body
- If you have a tumor in your brain you will have a brain MRI*

Every 12 weeks starting from Cycle 1 Day 1 through end of treatment (clinic visit)

- ECHO (echocardiogram) or MUGA (multiple gated acquisition) scan to measure how much blood your heart pumps out with each heartbeat

You may be participating in this study for as long as you tolerate the study tests, procedures, and study drugs (ONT-380/placebo, capecitabine and trastuzumab) and your disease is stable or improving. If you have cancer in your brain and in your body and progression occurs only in your brain you may be able to continue participating in this study and receiving the study drugs you are assigned to. If this occurs your doctor will discuss this with you.

Follow-up Period

30-Day Follow-up (clinic visit)

- You will be asked if you have any side effects or new medical problems and what they are*
- You will be asked about all medications you are currently taking*
- Physical examination
- Vital signs (blood pressure, heart rate, temperature, and breathing rate)
- 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)
- Tumor assessment by CT scan or MRI that takes cross-sectional pictures (slices) of your body
- MRI of your brain even if you don't have a brain tumor*
- Urine pregnancy test (not required for females of non-child-bearing potential or males). If the urine test is positive, a blood test will be done to confirm the result.*
- You may have an ECHO (echocardiogram) or MUGA (multiple gated acquisition) scan to measure how much blood your heart pumps out with each heartbeat*

Long-Term Follow-up (approximately every 3 months after the 30-Day Follow-Up Visit)

- This may be a phone call or a visit to the clinic to learn more about your cancer after the study treatment period has ended. You will be asked about the status of your

cancer, how you are feeling and about any new treatments you may have started since you stopped receiving the study drug combination you were assigned to. If you are unable to be reached, your medical records may be looked at to get this information.*

At any time during and after the study, you may have different or more tests and procedures if your study doctor thinks they are needed.

Potential Risks, Side Effects, Discomforts and Inconveniences

If you take ONT-380, capecitabine, and/or trastuzumab certain side effects and discomforts may happen after you take ONT-380, capecitabine and/or trastuzumab. ONT-380, capecitabine and/or 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.

The effect of ONT-380 on your skin's sensitivity to the sun is unknown. As a precaution, it is recommended that you limit sun exposure and use sunscreen.

Side effects associated with ONT-380 either alone or in combination with capecitabine and/or trastuzumab:

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

Most common, occurring in greater than 25% of subjects

- Constipation
- Diarrhea
- Fatigue or tiredness
- Nausea
- Rash, skin peeling, and skin redness
- Vomiting

Common, occurring in between 10% and 25% of subjects

- Abnormal liver function tests that may mean liver damage, or possible liver failure
- Cough
- Decreased appetite
- Dizziness
- Dry skin
- Headache
- Hot flush
- Indigestion
- Joint pain
- Muscle aches
- Night sweats
- Shortness of breath
- Urinary tract infection
- Upper respiratory tract infection
- Pain in the abdomen
- Pain in the back
- Pain in the chest
- Pain in the extremity

Rare but Serious

Hypokalemia (decrease in potassium levels) has been reported in patients taking ONT-380 in combination with ado-trastuzumab. There have been rare reports of mild heart failure (a decrease in ejection fraction) in patients taking ONT-380 in combination with trastuzumab alone as well as in combination with other cancer treatments. Damage to the lungs, another rare but serious potential side effect, has been reported with other HER2 inhibitor drugs, but has not been reported with ONT-380.

The Most Common Side Effects Reported in Patients Treated with Capecitabine:

- Capecitabine has different side effects that your study doctor will discuss with you

The Most Common Side Effects Reported in Patients Treated with Trastuzumab:

- Trastuzumab has different side effects that your study doctor will discuss with you

Other Risks

Blood Collection:
The risks of taking blood may include pain, redness, swelling and/or bruising where the needle enters your body, light-headedness and fainting. On rare occasions, local blood clot formation or infection with redness and irritation of the vein has occurred. The blood pressure cuff may cause discomfort or bruising to the upper arm.

Electrocardiogram (ECG):
An ECG is an electrical tracing of your heart's activity. During the procedure, you will have electrodes (small sticky patches) placed on your chest skin and wires attached to them. There may be some pulling on your skin or irritation, similar to pulling off an adhesive bandage, when the patches are removed.

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

Obtaining Archival Tumor Tissue (if your archival tumor tissue is available):
A sample of your original tumor tissue has previously been collected for another purpose and there is enough tumor tissue available for use in this pre-screening. Your study doctor will request that a small sample of your original tumor be sent to a laboratory for testing. There are no additional physical risks involved in this testing.

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

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

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

Reproductive Risks:
No information is available on the possible risks to a developing fetus when ONT-380 is taken by a pregnant woman or by a man whose female partner becomes pregnant. To prevent injury to an unborn child, you agree to make all efforts to prevent any possible pregnancy and agree to use a highly effective birth control (failure rate of less than 1%) while you are taking part in this study and for seven months after the last dose of the study drug combination you were assigned to. ONT-380 could harm an unborn child or nursing infant. If you complete the consent process, are eligible to participate in this study, and are a female who may become pregnant, then you must agree not to become pregnant and not to nurse a baby while you participate in this study and for seven months after your last dose of the study drug combination you were assigned to. If you are a male, you must agree not to get your partner pregnant while you participate in this study and you must agree to use birth control while you participate in this study and for seven months after your last dose of the study drug combination you were assigned to.

Acceptable birth control methods are: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; or sexual abstinence. Male patients with partners of childbearing potential must use barrier contraception.

If you do become pregnant, suspect you are pregnant, or if your partner becomes pregnant while you participate in this study or during the seven months after your last dose of the study drug combination you were assigned to, you must tell your study doctor immediately. If you become

pregnant, you will be taken off this study and you will be asked to provide information on the outcome of the pregnancy. Cases of pregnancy must be reported through seven months after the last dose of study drug, either ONT-380/placebo, capecitabine or trastuzumab, whichever is latest. Your doctor will ask for follow-up evaluation of the pregnancy, fetus, and child. Additional instructions for reporting the pregnancy and outcome will be provided at the time of notification.

Potential for Unknown/Additional Side Effects and Risks

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

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

Benefits

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

Economic Considerations

You will not be paid for taking part in this study. Tests and procedures that would be performed for your regular cancer care whether you are on this study or not are called "standard of care." All of the tests and procedures listed in this consent form that will be performed at your study visits are standard of care unless noted with an asterisk (*). There will be no charge to you or your insurance provider for tests or procedures noted with an asterisk as these are performed for study purposes only. There will be no charge to you or your insurance provider for the ONT-380 or placebo. For this study, capecitabine and trastuzumab are 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. All other tests and procedures will be charged to you or your insurance provider in the usual way as these are standard of care. This may include other tests and procedures not listed in this consent if your doctor feels it is necessary for your care, such as additional laboratory tests.

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

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

Your study doctor will receive direct and indirect payment from Cascadian Therapeutics, Inc. (the study sponsor) for their time spent doing research and general administrative services for this study. Cascadian Therapeutics, 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 the sponsor (Cascadian Therapeutics, Inc.) your bodily fluids and tissue samples collected during the study and any new drugs that may be developed from your fluids or samples.

Treatment Alternatives

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

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

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

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

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

The protected health information that will be collected in this study includes demographics, medical history, physical examinations, routine lab tests, review of adverse events and medications you take (past and present), vital signs, MRI scans, CT scans, ECHOs or MUGAs,

pregnancy tests, blood or tissue samples for research purposes, information recorded in study questionnaires, survival follow-up information and records about any study drug(s) that you received. This information will be recorded on forms provided by the sponsor. These forms are known as case report forms.

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

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

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

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

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

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee or Institutional Review Board that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential

- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The study doctor, Michael DiGiovanna, MD, PhD and the Yale study team
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Other federal regulatory or governmental agencies such as the National Cancer Institute/National Institutes of Health (NCI/NIH) and the Office for Human Research Protections (OHRP)
- The study sponsor or manufacturer of study drug, Cascadian Therapeutics, Inc., and/ or their representatives, affiliates, and collaborators
- People and companies with whom the sponsor works, such as clinical research organizations who help the sponsor manage the study
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study
- Independent committee of physicians and experts that will review safety information from this study periodically
- Individuals and businesses outside the hospital that provide services (for example, insurance companies, legal offices, and data storage companies)
- Medical information from this study may become part of your medical record at the clinic, and, in order to provide you with routine care, other people at the clinic may need to review the information we put into your record.

The sponsor and sponsor's authorized representatives will analyze and use the information they receive for the purposes of this study and to help establish whether the study drug reaches the appropriate standards of safety set by the authorities and also whether it is effective. Such purposes include:

- Conducting and overseeing the study
- Checking your suitability to take part in the study
- Monitoring your safety while you are receiving the study drug
- Comparing your response to the study drug with those of other participants in clinical studies
- Supporting the development of the study drug

- Supporting the licensing application, marketing, distribution, sale, and use of the study drug for global regulatory approval of the study drug anywhere globally

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

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

Those who receive your information may share it if they are required by law to do so. If you receive Medicare benefits and if the sponsor of this study pays for any study-related treatment, then complications or injuries, personal information about you, your treatment, and your participation in this study will be provided to the sponsor, who will provide it to Medicare to the extent required by law.

Authorized representatives of the Food and Drug Administration (FDA**)** and the manufacturer of the study drug being tested, Cascadian Therapeutics, Inc., may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality.

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

You have the right to review and copy your health information in your medical record throughout the study in accordance with institutional medical records policies.

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

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

Biomarker Testing

As a part of this study, your coded study information and samples will be used in research projects to see if there are biomarkers present in your samples that could predict whether or not ONT-380 combined with capecitabine and trastuzumab may be more or less effective. You will not benefit directly from this biomarker research; however, the information learned from the biomarker research may help develop better treatments for cancer in the future. The results of these biomarker tests will not be reported to you or your doctor and will not be used to make any decisions about your medical care. No genetic counseling will be offered or paid for by the sponsor. Information learned from the biomarker research will not be placed in your medical record. You will not be identified in any reports or publications resulting from the biomarker research. The results and other information from the biomarker research may be submitted to the FDA, or another government agency, and will identify you by your initials and subject identification number only.

There is a risk that your information could be misused. The chance of this happening is very small. We have protections in place to lower this risk. There can also be a risk in uncovering genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Very rarely, health or genetic information could be misused by employers, health insurance companies, and others. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers (except those with fewer than 15 employees) to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

In Case of Injury

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

If you become ill or are physically injured due to the study drug, ONT-380, or any investigational procedure specifically required by the plan for this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study drug, ONT-380, or properly performed non-standard of care investigational procedure required by the study will be covered by the Sponsor as long as you have followed the directions of the study doctor.

If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the study doctor.

You will not receive any other kind of payment. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study. You do not give up any of your legal rights by signing this consent form.

Voluntary Participation and Withdrawal

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

If you want to leave the study, you must let your study doctor know because your study doctor may need to do certain tests (such as blood tests) to ensure you may safely stop taking the study drug. Any study information about you that has already been collected will be sent to the sponsor.

Your study doctor may ask you to come in for more study visits after you decide to leave the study. If you agree, then your study doctor will collect information from those visits as well and will share this information with the sponsor of the study. Your doctor may also contact you for long term follow-up or look at your medical records to learn more about your cancer after the study treatment period has ended and will send that information to the sponsor unless you have told your doctor in writing that you do not want them to do that. The sponsor may share the information with the organizations described in the "Confidentiality and Authorization to collect, use and disclose Protected Health Information" section.

Withdrawing From the Study:
If you decide to participate in this research study, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, send or deliver a written notice to the study doctor, Dr. Michael DiGiovanna, at the address listed on page one of this form and tell them that you no longer want to take part. They will make sure that proper procedures are followed and a final visit is made for your safety. This will cancel any future research study appointments. If you request to withdraw from the study, you will not lose any benefits, medical treatment or legal rights to which you are otherwise entitled.

The researchers may withdraw you from participating in the research if necessary. Your study doctor may take you off this study without your consent, and the study drug may be stopped if:

- Your study doctor feels that it is in your best medical interest

- Your condition gets worse
- You have serious side effects
- You are unable, unwilling, or have failed to follow the directions given to you by your study doctor
- You develop a serious illness or injury, even if it is not related to your taking part in the study
- New information becomes available that shows this study is not the best option for you
- You become pregnant, or you are nursing a child, during this study
- The sponsor (Cascadian Therapeutics, Inc.), the FDA, the Institutional Review Board (IRB), or other regulatory agencies decide to stop the study before the study is done, which could happen without warning

If any of these events happen, your study doctor will talk with you about other treatment options that are available and assist with the plans for your continued care, as appropriate.

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

If you fail to give your consent by not signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study. Unless and until you do cancel the consent, it will remain valid and effective.

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

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

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

Authorization and Permission

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

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

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

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

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

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