THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

A Pilot single Arm Open Label Trial Evaluating Bintrafusp (Anti-PD-L1/TGF-Beta TRAP) in a Window Setting in Patients with Stage II-III HER2/neu Positive (HER2+) Breast Cancer (BC)
2017-0502

Study Chair: Rashmi K. Murthy

_____ _____
Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

STUDY SUMMARY

The goal of this clinical research study is to learn if giving bintrafusp (M7824; MSB0011359C) to patients with Stage II or III HER2+ breast cancer who are scheduled to receive chemotherapy and have surgery as part of their standard care can change how many tumor-infiltrating lymphocytes (TILs) are near the tumor. TILs are a type of white blood cell that is related to your immune system.

The safety and tolerability of bintrafusp will also be studied.

This is an investigational study. Bintrafusp is not FDA approved or commercially available. It is currently being used for research purposes only. The study doctor can explain how the study drug is designed to work.

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. If you take part in this study, you may not be able to receive standard options for treatment.

You can read a list of potential side effects below in the Possible Risks section of this consent.

You may receive 2 doses of bintrafusp while you are on study.

Bintrafusp will be provided at no cost to you while you are on study. You and/or your insurance provider will be responsible for the cost of chemotherapy and surgery as part of your standard care.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard drugs and/or surgery without taking part in this study to treat the disease. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. The following screening tests will be performed to help the doctor decide if you are eligible.

- You will have a physical exam.
- You will have a skin exam to check for any skin rashes.
- You will have an eye exam by an eye doctor.
- You will have an EKG and echocardiogram (ECHO) to check your heart function
- Blood (about 4½ tablespoons) will be drawn for routine testing (which may include checking your blood sugar levels and measuring your hormone levels), to test for hepatitis B and C, HIV, and tuberculosis (TB), and for immune system testing.
- Urine will be collected for routine tests.
- You will have a mammogram and ultrasound of your breast and the area under your arm to check the status of the disease.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for pregnancy test within 72 hours before the first dose of study drug(s). To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Up to 20 participants will be enrolled at MD Anderson. All will take part at MD Anderson.

Study Drug Administration

If you are found to be eligible to take part in this study, you will receive bintrafusp by vein over 1 hour on Days 1 and 15 of the study. You will be watched in the clinic for 2 hours after the infusion to check you for any side effects.

After your last dose of bintrafusp, you will receive chemotherapy during Days 28-56. The study doctor will tell you what type of chemotherapy you will receive and you will sign a separate consent form describing how it is given, when it is given, and its risks.

Within 56 days after completing chemotherapy, you will have your scheduled surgery. You will sign a separate consent form describing the surgery and its risks.

Length of Study

You may receive 2 doses of bintrafusp while you are on study. You will no longer be able to take the study drug if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation in this study will be over after you have had surgery.

Study Visits

On **Day 1:**

- You will have a physical exam.
- You will have a skin exam.
- You will have an EKG.
- Blood (about 4½ tablespoons) will be drawn for routine tests and immune system testing.
- Urine will be collected for routine tests.
- Blood (about 1½ teaspoons) will be drawn for pharmacokinetic (PK) and antibody testing. PK testing measures the amount of study drug in the body at different time points. Antibodies are created by the immune system and may attack foreign cells or substances, such as the study drug.
- You will have a core tumor biopsy to test for immune cells and biomarker testing, including genetic biomarkers. Biomarkers are found in the blood and tissue and may be related to your reaction to the study drugs. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge. In most cases, the affected area will be numbed with anesthetic.

On **Day 15:**

- You will have a physical exam.
- You will have a skin exam.
- You will have an EKG.
- Blood (about 4½ tablespoons) will be drawn for routine tests and immune system testing.
- Urine will be collected for routine tests.
- Blood (about 1½ teaspoons) will be drawn for PK and antibody testing.

On **Day 28:**

- You will have a physical exam.
- You will have a skin exam.
- You will have a breast ultrasound.
- You will have an ECHO.
- Blood (about 5 tablespoons) will be drawn for routine, PK, and immune system testing.
- Urine will be collected for routine tests.
- You will have a core tumor biopsy to test for immune cells and biomarker testing, including genetic biomarkers.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for pregnancy test

On **Day 118:**

- You will have a physical exam.
- You will have a skin exam.
- Blood (about 4½ tablespoons) will be drawn for routine tests and immune system testing.
- Urine will be collected for routine tests.
- You will have an EKG.

At any time on study, if the doctor thinks it is needed, you will have an EKG and/or eye exam.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Any live vaccine therapies for the prevention of infectious disease is not allowed during the 30 days before your first dose of study drug and while you are on study. Inactivated vaccines (such as inactivated influenza vaccines) are allowed**.**

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs and procedures.

Receiving the study drugs as part of this study may affect your ability to receive chemotherapy and/or surgery in the future. The study drugs may also change the effectiveness of future chemotherapy you may receive.

Bintrafusp **(M7824;MSB0011359C) Side Effects**

Common (occurring in more than 20% of patients)

• diarrhea	• nausea	• infusion reaction (possible chills and/or hives)

Bintrafusp may cause low blood cell counts (red blood cells). A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.

Occasional (occurring in 3-20% of patients)

• fatigue • skin rash/itching • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • high blood sugar (possible diabetes)	• low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • low blood levels of potassium (possible weakness and/or muscle cramps)	• mucosal bleeding (mouth/gums) • blood in the urine • loss of appetite • abnormal liver tests • weakness • nosebleed • coughing up blood • difficulty breathing

Bintrafusp may cause the development of a new type of cancer (such as keratoacanthoma, a type of skin cancer).

Rare but serious (occurring in fewer than 3% of patients)

• heart inflammation • skin sores • decreased production of adrenal hormones (possible weakness and/or low blood pressure)	• overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating) • inflammation of the liver	• muscle/joint inflammation • joint pain/swelling • eye inflammation • lung inflammation (possible difficulty breathing)

In patients with liver cancer, bintrafusp may cause an increased risk of tumor bleed. Tell the doctor right away if you have abdominal pain, nausea/vomiting, light headedness or abdominal swelling.

Bintrafusp may also cause certain immune-related side effects, such as:

- damage to the nervous system (causing numbness and/or paralysis)
- inflammation of the pancreas (possible abdominal pain)
- inflammation inside the eye (possible vision problems)
- immune response (causing muscle weakness)

Using the study drug in combination with chemotherapy may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

The type of **genetic testing** being performed in this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks
Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must agree to use highly effective birth control methods during the study if you are sexually active.

Birth Control Specifications: Birth control methods considered as highly effective:

- Combined (estrogen and progesterone containing) hormonal birth control that stops ovulation (pills, intravaginal, patches)
- Progesterone-only hormonal birth control that stops ovulation (pills, injections, implants)
- Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion ("tubes tied")
- Vasectomized partner

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, a stool sample will be collected from you at screening for microbiome testing (a type of testing that checks for certain bacteria and

microorganisms in the body). You will also complete a questionnaire about your diet. It should take about 10-15 minutes to complete.

Optional Procedure #2: If you agree, you will have a cheek swab for microbiome testing. To collect this sample, a cotton-tipped applicator will be brushed back and forth over the inside of your cheek.

There are no benefits to you for taking part in the optional procedures. Future patients may benefit from what is learned. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedures.

Optional Procedure Risks:
Providing a **stool sample** may be uncomfortable.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns about completing the questionnaire, you are encouraged to contact your doctor or the study chair.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

Circle your choice of "yes" or "no" for each of the following optional procedures:

Optional Procedure #1: Do you agree to give a stool sample for microbiome testing and complete a questionnaire about your diet?

YES **NO**

Optional Procedure #2: Do you agree to have a cheek swab for microbiome testing?

YES **NO**

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or EMD Serono for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However,

your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Rashmi K. Murthy, at 713-792-2817) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, EMD Serono, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: EMD Serono.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Your personal information and/or samples are being collected as part of this study. These data and/or samples may be used by researchers at MD Anderson or shared with other researchers and/or institutions for use in future research.

Before being shared for future research, every effort will be made to remove your identifying information from any data and/or samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data or samples are used for future research. If this research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research

Samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you. The same level of data protection that covers your individual data does not apply to summary results (when data from the whole study is combined).

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s).

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and

study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:

- Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
- The IRB and officials of MD Anderson
- EMD Serono, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

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

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

_____ _____
SIGNATURE OF LAR DATE

_____
PRINTED NAME and RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol **2017-0502**.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION DATE
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN,
OR STUDY CHAIR)

_____
PRINTED NAME OF WITNESS TO THE VERBAL TRANSLATION