THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

A "Window of Opportunity" Phase I Trial of Focal Radiotherapy and bintrafusp alfa in patients with advanced intrahepatic cholangiocarcinoma

2020-0899

Study Chair: Eugene Koay

_____ _____
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 bintrafusp alfa can be safely given in combination with radiation therapy to patients with metastatic (has spread to other parts of the body) bile duct cancer. The effects of this combination on the disease will also be studied.

This is an investigational study. Bintrafusp alfa is not FDA approved or commercially available. It is currently being used for research purposes only. The radiation therapy used in this study is delivered using FDA approved and commercially available methods. It is considered investigational to give radiation therapy in combination with bintrafusp alfa to bile duct cancer patients. The study doctor can explain how the study drug and radiation therapy are designed to work.

The combination of bintrafusp alfa and radiation therapy 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 are not from the Houston area, taking part in this study may require a prolonged stay out of town.

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

You may receive up to 15 doses of radiation therapy. You may receive bintrafusp alfa for up to 2 years. You will be in this study for up to 5 years including follow-up after you enroll in this study.

Bintrafusp alfa will be provided at no cost to you. You and/or your insurance provider will be responsible for the cost of the radiation therapy.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive radiation therapy outside of this study. You may choose to receive other investigational therapy, if available. Also, patients with FGFR genetic alterations, high tumor mutational burden, high microsatellite instability, deficient mismatch repair, or NTRK fusions have targeted treatment options that are different from bintrafusp alfa. 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. You will have a screening visit to help the doctor decide if you are eligible. The following tests and procedures will be performed at this visit:

- You will have a physical exam.
- Blood (about 4 tablespoons) will be drawn for routine tests and biomarker tests. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug.
- A stool sample will be collected for biomarker testing.
- You will have a CT scan, MRI, or PET/CT scan to check the status of the disease.
- If the doctor thinks it is safe to do so, you will have a core biopsy for biomarker testing. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge.
- If you have leftover tumor tissue from a previous procedure, it will also be collected for biomarker testing.
- If the doctor thinks it is needed, you will have an EKG to check your heart function.
- If you can become pregnant, part of the above blood sample or a urine sample will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

This screening visit may be performed in the clinic or remotely using an approved video call platform (such as Zoom or Facetime) if you are unable to come to the clinic. If you have a remote screening visit, some of the above tests and procedures may not be required, and the blood draw and imaging scans may be performed at a laboratory closer to your home. If you are unable to come to the clinic, the study doctor will discuss this with you.

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 this study, you will not be enrolled. Other options will be discussed with you.

Study Groups

If you are found eligible to take part in this study, you will be assigned to a dose level of radiation therapy based on when you join this study. Up to 3 dose levels of radiation therapy will be tested. Up to 6 participants will be enrolled at each dose level. The first group of participants will receive the highest dose level of radiation therapy. If intolerable side effects are seen, the next group of participants will receive a lower dose than the group before it. If intolerable side effects are seen in the second group, the next group of participants will receive a lower dose. Researchers want to find the highest tolerable dose of radiation therapy to give in combination with bintrafusp alfa.

All participants will receive the same dose level of bintrafusp alfa.

Up to 12 participants will take part in this study. All will be enrolled at MD Anderson.

Study Drug Administration

You will receive radiation therapy **1 time a day on weekdays (Monday-Friday) for up to 15 doses (about 3 weeks).** Before your first dose of radiation therapy, you will have a CT scan to help plan your radiation treatment.

Starting 1 week after you complete radiation therapy, you will receive bintrafusp alfa by vein over about 1 hour every 2 weeks.

You will no longer be able to take the study drug and radiation therapy 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 the follow-up visits.

Study Visits

During **Weeks 1-5, 7, 9, 11, and 12,** you will have study visits. The following tests will be performed at these visits:

- You will have a physical exam.
- Blood (about 4 tablespoons) will be drawn for routine tests.

Additional tests will also be performed only at certain visits:

- During **Weeks 2, 4, 9, and 12**, blood (about 4 tablespoons) will be drawn for biomarker tests.
- During **Weeks 4, 9, and 11**, stool will be collected for biomarker tests.
- During **Weeks 4 and 9**, you will have a core tumor biopsy for biomarker tests.
- **Every 12 weeks**, you will have a CT scan, MRI, and/or PET-CT scan to check the status of the disease.

Every 3-4 months while you receive bintrafusp beyond Week 12, then for up to 1 year after you complete all study therapy, you will have follow-up study visits. At each of these visits, the following tests will be performed:

- You will have a physical exam.
- Blood (about 4 tablespoons) will be drawn for routine tests.
- You will have a CT scan, MRI, and/or PET-CT scan to check the status of the disease.

If you are unable to come to the clinic for any of these visits, they may be performed remotely by phone, mail, email, or an approved video call platform. These meetings should take about 15 minutes. If so, some of the above tests and procedures may not be required. You may also have your blood draws and imaging scans performed at a laboratory closer to your home. If you are unable to come to the clinic, the study doctor will discuss this with you.

Other Information

The study team will collect information from your medical record before, during, and for up to 5 years after you complete radiation therapy during this study. This information will be related your personal medical history, diagnosis, and the treatment you received or are scheduled to receive for head and neck cancer.

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.

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

Radiation Therapy Side Effects

It is not known how often the side effects of radiation therapy may occur. The following risks are for radiation with photons or protons.

• fatigue • swelling • swelling of the arms or torso • skin changes (possible dryness, itching, peeling, and/or blistering) • hair loss at the treatment site	• mouth problems • trouble swallowing • stomach and/or small intestine ulcer • abdominal pain • nausea • vomiting • diarrhea • bleeding	• blood vessel damage • abnormal liver function • damage to the ribs • urinary and/or bladder changes • sexual changes • inability to produce children • joint problems • secondary cancers

Radiation therapy may cause you to develop another type of cancer. Side effects may not occur for up to 6 months after radiation therapy is over.

Bintrafusp Alfa Side Effects

Common (occurring in more than 20% of patients)

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

Bintrafusp alfa may cause a low red blood cell count. 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 alfa may cause the development of a new type of cancer (such as keratoacanthoma and/or squamous cell carcinoma, types of skin cancer).

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

• heart inflammation • skin sores	• overactive thyroid gland (possible	• muscle/joint inflammation

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

In patients with liver cancer, bintrafusp alfa 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.

Three clinical research studies in two types of cancers (a type of lung cancer called NSCLC and biliary tract cancer) have been recently stopped because bintrafusp alfa was not shown to be more effective than other available therapies when given to these patients. In some patients in these studies, the patients' tumors continued to grow, which resulted in death in some cases. It is possible that the symptoms of your condition will not improve during the study or may even get worse and/or result in death.

Using the study drug and radiation therapy together may cause side effects that are not seen when each is given alone. The study 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.

Providing a **stool sample** may make you feel embarrassed or uncomfortable.

CT scans send x-rays through the body at many different angles. You will be exposed to a small dose of radiation. All radiation adds up over a lifetime and may increase the risk of new cancer forming. Some people may feel "closed in" while lying in the scanner. However, the scanner is open at both ends, and an intercom allows you to talk with doctors and staff. If you feel ill or anxious during scanning, doctors and/or radiology technicians will give comfort, or the scanning will be stopped. Solution may also be given by vein to make the x-ray pictures more accurate. This may cause flushing, nausea, and/or severe allergic reactions. The solution injection may also cause pain, bleeding, bruising, hives, and/or itching.

During the **MRI**, you may feel mild vibrations throughout your body. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect

your ears. Some people, especially those who tend to feel uncomfortable in small or closed spaces, may feel “closed in” and become anxious while in the scanner. The scanner has an intercom, which will allow you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish. The MRI will require a catheter to be inserted into one of your veins in order to inject the MRI contrast agent. This may cause skin irritation, bleeding, and/or infection. You may have an allergic reaction to the contrast agent.

The magnetic field used in MRI scanning may harm you if you have certain types of metal in your body (as might be found in pacemakers, neurostimulators, or certain clips). It may cause problems with devices, such as pacemakers. If you have metal in your body or devices such as a pacemaker, you should discuss this with the study doctor.

Although every effort will be made to keep **study data** safe, there is a chance that your personal health information could be lost or stolen. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study. There will be no personal identifying information connected to your questionnaire answers.

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 use birth control during the study if you are sexually active.

Birth Control Specifications: If you can become pregnant or father a child, you must use 2 highly effective birth control methods during the study and for 90 days after your last dose of study drug. Highly effective birth control methods include:

- Hormonal methods such as birth control pills, implants, or injections
- Copper intrauterine devices (IUDs)
- Male or female condoms used with spermicide
- Bilateral tubal ligation (“tubes tied”) or bilateral salpingectomy (removal of both fallopian tubes)
- Vasectomy of your partner

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy. You must not donate sperm during the study and for 125 days after the last dose of study drugs.

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 may result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If the disease gets worse and you agree, you will have a core tumor biopsy for biomarker testing.

Optional Procedure #2: If the disease gets worse and you agree, blood (about 4 tablespoons) will be drawn for use in additional future research related to the study drug and/or the disease.

You do not have to take part in the optional procedures to take part in the main study. 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

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.

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.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

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

Optional Procedure #1: If the disease gets worse, do you agree to have a core tumor biopsy for biomarker testing?

YES **NO**

Optional Procedure #2: If the disease gets worse, do you agree to have additional blood drawn for use in additional future research related to the study drug and/or the disease?

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. Eugene Koay, at 713-563-2381) 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, 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

Data

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

Samples

Samples (such as blood and/or tissue) are being collected from you as part of this study. Researchers at MD Anderson may use any leftover samples that are stored at MD Anderson in future research. Leftover samples stored by EMD Serono may be used in future research.

Before being used or shared for future research, every effort will be made to remove your identifying information from any data and/or research 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 research samples are used for future research. If future 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 research 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

Research samples collected from you as part of this study may 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.

Conflict of Interest

The Proton Therapy Center is owned by a group of investors, including MD Anderson. Because of this, MD Anderson will receive a share of the financial benefit from the use of the Proton Therapy Center.

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.

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 **2020-0899**.

_____ _____
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