THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Phase I/II Trial of Bintrafusp Alfa (M7824) and Pimasertib for Treatment of Intracranial Metastases

2019-1091

Study Chair: Hussein Tawbi, M.D., Ph.D

_____ _____
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

There are 2 parts to this study: Part 1 (dose escalation) and Part 2 (dose expansion).

The goal of Part 1 of this clinical research study is to find the highest tolerable dose of pimasertib and bintrafusp alfa (also called M7824) that can be given to patients with melanoma, lung, or breast cancer that is metastatic (has spread).

The goal of Part 2 of this study is to learn if the dose of pimasertib together with bintrafusp alfa found in Part 1 can help to control metastatic melanoma, lung, or breast cancer.

In both parts of the study, researchers also want to learn more about the safety and effects of this combination.

This is an investigational study. Bintrafusp alfa and pimasertib are not FDA approved and commercially available. It is investigational to give the drugs in combination. The study doctor can explain how the study drugs are designed to work.

The study drugs may help to prevent or delay the disease from progressing (getting worse) and/or coming back. Future patients may benefit from what is learned in this study. 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 experience side effects, some of which may be severe or fatal.

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

You may receive the study drugs for up to 1 year.

Bintrafusp alfa and pimasertib will be provided during the study at no cost to you. When the study ends, the sponsor will not continue to supply study drug to you. If you are prescribed the drugs after the study ends, you and/or your insurance provider will be responsible for their cost.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard therapy for 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 Visit

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

- You will have a physical exam.
- You will have a neurocognitive exam (tests to check your memory and thinking abilities, for example).
- You will have an eye exam by an eye doctor.
- You will have an EKG and either an echocardiogram (ECHO) or MUGA scan to check your heart function.
- Blood (about 4½ tablespoons) will be drawn for routine tests (including tests for hepatitis and HIV), biomarker testing, genetic testing, pharmacokinetic (PK) testing, antibody testing, and for tests of the immune system. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug. Genetic testing is being done so researchers can learn if the differences in genetic material (such as DNA and RNA) are also linked to your response to treatment. 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.
- Urine will be collected for routine tests.
- Leftover tumor tissue from a previous biopsy or surgery will be collected for genetic and biomarker testing.
- If you have a tumor that can be biopsied safely, you will have a tumor biopsy for genetic and biomarker testing. The study doctor will tell you what type of biopsy you will have based on where the tumor(s) is located.

- You will have an MRI to check the status of the disease.
- If you can become pregnant, blood (about ½ teaspoon) or urine will be collected for a pregnancy test. 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.

Study Groups

If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up 3 groups of 6 participants will be enrolled in Part 1 of the study, and up to 24 participants will be enrolled in Part 2. Up to 36 participants will be enrolled in this study. All will take part at MD Anderson.

If you are enrolled in Part 1, the dose of pimasertib you receive will depend on when you join this study. The first group of participants will receive the lowest dose level of pimasertib. Each new group will receive a higher dose of pimasertib than the group before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of pimasertib is found.

If you are enrolled in Part 2, you will receive pimasertib at the highest dose that was tolerated in Part 1.

The study doctor will tell you what dose of bintrafusp alfa you will receive.

Study Drug Administration

If you are found to be eligible to take part in this study, you will receive bintrafusp alfa every 2 weeks by vein over about 1 hour.

You will take pimasertib by mouth 2 times at about the same time every day, about 12 hours apart (1 dose in the morning, 1 dose in the evening). Take the dose with a cup (about 8 ounces) of water either 2 hours before a meal or 1 hour after a meal.

You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Study Visits

You will come to the clinic on **Day 1 of every cycle.** At these visits, some or all of the following tests/procedures may be performed (depending on the visit). Your study visit schedule will be discussed with you in more detail.

- You will have a physical exam.
- Blood (up to 4½ tablespoons) will be drawn for routine tests, biomarker testing, and for tests of the immune system.

- Blood (about 2 teaspoons) will be drawn for PK testing and antibody testing before the dose of study drugs (Cycles 1-3 and 6). Blood will also be drawn after the dose during Cycles 1 and 3.
- Urine will be collected for routine tests.
- You will have an ECHO or MUGA scan to check your heart function (even-numbered cycles only).
- You will have a tumor biopsy to compare against the tissue collected at screening in order to learn if the study drugs have had an effect on the disease (Cycle 2 only). The study doctor will tell you what type of biopsy you will have.
- You will have a spinal tap to collect a small sample of cerebrospinal fluid (CSF, the fluid that surrounds the spine) for biomarker testing and to check the status of the disease (Cycles 1, 3, and 6 only). A spinal tap (also called a lumbar puncture) is when fluid surrounding the spinal cord is removed by inserting a needle into the lower back. The affected area is numbed with local anesthetic during the procedure.
- If you can become pregnant, blood (about ½ teaspoon) or urine will be collected for a pregnancy test.

In addition to the above, during **Cycles 1-3 and then every other cycle after that for 1 year,** you will have an MRI to check the status of the disease. After 1 year, this will be done every 3 cycles. If the doctor thinks it is needed, you may have this scan more or less often (depending on how you are responding to the study drugs).

End-of-Treatment Visit

As soon as possible after your last dose of study drugs:

- You will have a physical exam.
- You will have a neurocognitive exam.
- You will have an ECHO/MUGA.
- You will have an eye exam to check your vision.
- Blood (about 4 tablespoons) will be drawn for routine tests, PK testing, antibody testing, biomarker testing, and tests of the immune system. Please note that blood for PK and antibody testing will only be done if you stopped taking the study drug before Cycle 6.
- Urine will be collected for routine tests.
- You may have an MRI to check the status of the disease (depending on when your last scan was done).
- If you can become pregnant, blood (about ½ teaspoon) or urine will be collected for a pregnancy test

Follow-Up

About 30 days after your last dose of study drugs, you will be called and asked how you are feeling and if you have had any side effects. This call should last about 5 minutes.

If you stopped taking the study drugs for reasons other than the disease getting worse, you will have follow-up visits **every 6 weeks for the first year and then every 12 weeks after that for up to 2 years**. At each visit, you will have a physical exam and blood will be drawn for routine tests. You may be called by the study staff to ask how you are doing at these time points if you cannot come to the clinic.

For all participants, you will be called **every 12 weeks** until the study ends. During each call, you will be asked how you are doing and if you have started any new medications or treatments. Each call should last about 5-10 minutes.

Additional Information

You may not take certain drugs while you are taking the study drugs and you may not take any herbal drugs. Talk with the study doctor about any drugs you are currently taking and before you start any new drugs. You will also be provided with a document that lists the types of drugs that should be avoided while you are on study.

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 drugs and procedures.

Bintrafusp alfa and pimasertib may cause low blood cell counts (red and/or white blood cells).

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Bintrafusp Alfa Side Effects

Common (occurring in more than 20% of patients)

• diarrhea	• nausea • low red blood cell count	• infusion reaction (possible chills and/or hives)

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 or squamous cell carcinoma, types 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 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.

<u>Pimasertib Side Effects</u>

This is an early study of pimasertib in humans, so the side effects are not well known. Based on early human studies and risks seen in similar drugs, pimasertib may cause the following side effects:

• swelling (hand/arm/leg/face) • irregular heartbeat • decrease in heart pump function • fatigue • skin changes (such as skin rash, dry skin, and/or acne) • low blood levels of sodium (possible headache, confusion, seizures, and/or coma)	• dehydration • nausea • vomiting • diarrhea • sores and/or blisters in the mouth and esophagus (possible pain and/or difficulty swallowing)	• abnormal liver tests (possible liver damage) • muscle weakness, inflammation, damage, and/or breakdown • kidney damage/failure • abnormal vision (such as blurry vision and/or loss of vision) • blockage of a vein in the eye (possible

		blindness) • bleeding in the eye

If you have had hepatitis C (liver inflammation) in the past, taking pimasertib may cause the hepatitis to come back.

Using the study drugs together 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. The combination of bintrafusp alfa and pimasertib may cause the following additional side effects:

• abnormal EKG • blood clots in a vein (possible pain, swelling, and/or redness) • bleeding in or around the brain • worsening of existing diabetes	• liver bleeding • hole in intestine (possibly leaking contents into the abdomen) • inflammation of the intestines	• blockage in the lung (possible pain and/or shortness of breath) • reaction related to low white blood cell counts (possible dehydration, chills, kidney failure, and/or fainting)

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.

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, you must use a highly effective method of birth control while on study and for 24 weeks after your last dose of study drug. Highly effective methods include:

- Progestogen-only hormonal birth control that stops ovulation

- Hormonal methods including birth control pills, vaginal ring, injections, implants, patches, and intrauterine hormone-releasing system (IUS).
- Sterilization of yourself or your partner
- Intrauterine device (IUD)

If you can father a child, you must use a condom (female partner must also use an acceptable form of birth control) while on study and for 33 weeks after your last dose of study drug. You must let your sexual partners know that you are on in this research study and that birth control is required. You must not donate sperm.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy. If your partner/spouse becomes pregnant while you are on this study, the sponsor would like to collect information about the pregnancy. The study sponsor's contact information will be made available so that, if you and your partner wish to, you can share information about the outcome of the pregnancy with the sponsor. If you and/or your partner choose not to share this information, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

Females: You should not breastfeed while taking the study drug or for up to 24 weeks after the last dose of study drug. 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. The sponsor will ask for information about the pregnancy.

Getting pregnant may result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, you will have a tumor biopsy on Day 1 of Cycle 5 to check the status of the disease. This may help researchers understand how the study drugs are or are not affecting the disease. The study doctor will tell you what type of biopsy you will have.

Optional Procedure #2: If you agree, tumor tissue that is left over from your diagnosis and/or other procedures performed outside of this study will be collected and stored in a research bank at MD Anderson for use in future research related to cancer.
Before your samples can be used for research, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson. The IRB is a committee of doctors, researchers, and community members. The IRB is responsible for protecting study participants and making sure all research is safe and ethical.

Your samples will be given a code number. No identifying information will be directly linked to your samples. Only the researcher in charge of the bank will have access to the code numbers and be able to link the samples to you. This is to allow medical data related to the samples to be updated as needed.

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.

MD Anderson and others can learn about cancer and other diseases from **your banked samples.** In the future, people who may do research with these samples may need to know more information about your health. This information may be collected from your medical record. MD Anderson will make reasonable efforts to preserve your privacy, but cannot guarantee complete privacy. Sometimes your samples may be used for genetic research about diseases that are passed on in families. **Genetic research** may result in the development of beneficial treatments, devices, new drugs, or patentable procedures. There are no plans to provide you compensation from such developments. The results of any genetic tests may be put in your health records. If this information were released, it could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty obtaining insurance coverage and/or a job.
If you withdraw your consent to the storage of leftover samples in the tissue bank, then they will no longer be collected for storage. Any of your samples that remain in the tissue bank will no longer be used for research and will be destroyed.
However, if any of your de-identified samples were already released for research purposes before you withdrew consent, MD Anderson will not be able to destroy them.

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 have a tumor biopsy on Day 1 of Cycle 5 to check the status of the disease and tests to help researchers understand how the study drugs may have affected the disease?

YES NO

Optional Procedure #2: Do you agree to allow previously collected samples to be collected and stored in a research bank at MD Anderson for use in future research related to cancer?

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. Hussein Tawbi, at 713-792-2921) 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

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.

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 maybe 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).

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 **2019-1091.**

_____ _____
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