PRINCIPAL INVESTIGATOR: Charalampos Floudas, MD, DMSc, MS

STUDY TITLE: Phase 2 Study of **B**intrafusp **a**lfa in **R**ecurrent/Metastatic **O**lfactory **N**euroblastoma (BARON)

STUDY SITE: NIH Clinical Center

Cohort: Affected Participants

Consent Version: 09/27/2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

You can contact Dr. Charalampos Floudas, MD, at [redacted]

KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to join this study because you have metastatic Olfactory Neuroblastoma (ONB, also known as esthesioneuroblastoma). It is a kind of rare cancer which appears on the roof of the nasal cavity and can spread to other body parts.

The purpose of this study is to find a better way to treat ONB. We want to see if giving immunotherapy drug bintrafusp alfa, also known as M7824, can help your cancer shrink or disappear. Your study doctor thinks this study may be an option for you.

Bintrafusp alfa is a drug that blocks pathways that cancer cells use to prevent your immune system from fighting your cancer. Bintrafusp alfa has not been used to treat your type of cancer before, therefore we do not know whether or not it will work.

Bintrafusp alfa has been tried in other types cancers. Recently, the manufacturer of the drug closed 3 large studies because the drug was shown not to help those patients more than standard therapies. In addition, in some cases it seemed like the drug might make the cancer grow faster. However, the type of cancer treated in those studies was not the same as your cancer.

Bintrafusp alfa is not FDA approved. The use of this drug in this study is considered investigational, which means that this drug has not been approved by the FDA to treat any cancer. However, the FDA has given us permission to use bintrafusp alfa in this study.

There are other drugs that could be used to treat your disease, and these can be given by your regular cancer doctor if you do not take part in this study. For example: chemotherapy agents (platinum-based chemotherapy different than the one you have received, cyclophosphamide with vincristine and doxorubicin - CVP) are some possible treatments that you could receive.

The treatment being given in this study and the side effects are different than if you were to receive other forms of standard care. For example, platinum agents can cause nausea and vomiting, kidney damage, and low blood cell counts, while CVP can cause nausea or vomiting, low blood counts, constipation, peripheral neuropathy, hair loss, heart dysfunction, bladder irritation and bleeding. Bintrafusp alfa, belongs to a group of drugs called immunotherapy and may have different side effects related to inflammation (i.e., rash), diarrhea, fevers and bleeding.

If you decide to join this study, here are some of the most important things that will happen:

- Bintrafusp alfa will be given 1200 mg every 2 weeks for 26 doses.
- You will be seen in the NIH Clinical Center by your study team every 2 weeks while you are receiving treatment. These clinic visits will take 4-6 hours.
- When your treatment is stopped/finished, you will be seen in the NIH Clinical Center by your study team after 28 days from the last dose of drug. If you decide to discontinue treatment earlier than the planned 26 doses, you will be seen in the NIH Clinical Center by your study team within 14 days from the last dose of drug. If you cannot return to the Clinical Center for this visit, you may be assessed by telephone/email for adverse events. Also, a request can be made to collect required clinical labs from a local physician if required.
- After therapy is completed, you will continue to be seen every 3 months. You will have tests done (physical exams, blood work and scans) to see how you are doing and to see how your disease is responding. We will also collect samples from you (such as: blood and tissue samples) for research purposes.

As described above and later in more detail in this consent form, you may have side effects if you take part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death.

The most frequent side effects of bintrafusp alfa are problems with the immune system getting overactivated and acting up against parts of your body, and bleeding. Risks are explained in detail later in consent. Please talk to your study doctor or other members of the study team if you have any questions regarding risks or alternative treatments.

Just as we do not know what side effects you might have; we cannot know if you may benefit from taking part in this study. If you do not benefit, this study and the results from our research will help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you

about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and, you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn if giving immunotherapy drug bintrafusp alfa can help your cancer shrink or disappear. Prior clinical studies with bintrafusp alfa have helped researchers learn about the recommended dose that are safe when bintrafusp alfa is given to treat other cancers.

If you decide to join this study, you will receive bintrafusp alfa at the safe dose.

WHAT WILL HAPPEN DURING THE STUDY?

Before you begin the study

Before beginning the study, you will be evaluated by a physician investigator, as well as other members of the research team for eligibility to participate in the study. We will discuss your medical history in detail and draw blood from a vein to perform laboratory tests to help determine whether you are eligible to participate. These tests and/or procedures will help your doctor verify whether you can participate. This is called screening. The exams, tests, and procedures you will have are part of the usual approach for people who have ONB. We will discuss these tests and the reasons they are required if you need to have them. Most scans must be performed within 28 days before initiation of study therapy. Briefly, these tests, which will be performed include:

- Confirmation of diagnosis (The tissue may be from a previous surgery or biopsy. If tissue/report is not available, a biopsy may be performed to confirm the diagnosis).
- Physical examination, including height, weight, and vital signs. We will review any past or current medical conditions, medicines you are taking and cancer history. A review of your symptoms and your ability to perform your normal activities will also be done.
- Electrocardiogram (EKG – a record of your heartbeat) to evaluate your heart
- Imaging Assessments

- Computed tomographic scans (CT) that produce a picture of your body using a small amount of radiation to produce an image of your chest, abdomen, and pelvis. MRI can be done if clinically indicated.
- Brain MRI scan with contrast, if clinically indicated.
- PET/CT, if clinically indicated.
- Nuclear bone scan, if clinically indicated.

- Lab blood and urine tests
  - Routine and urine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, and other organs are working well as well as tumor markers
  - Urine or Serum pregnancy test
    If you are pregnant, you will not be able to take part in this study.
  - Tests for Hepatitis B and Hepatitis C.
    If you are having Hepatitis B and Hepatitis C viral infection, you will not be able to take part in this study.
  - HIV testing: As part of this study, we will test you for infection with HIV, the virus that causes AIDS. If you are infected with HIV, you may still be able to take part in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infections, and the importance of informing your partners at possible risk because of your HIV infection.

During the study

Day 1 (before starting the study drug bintrafusp alfa)

These tests will not be repeated if done within 28 days before you start the study therapy

- Physical examination, including weight, vital signs, and medical history.
- Imaging Assessments
  - Computed tomographic scans (CT) that produce a picture of your body using a small amount of radiation to produce an image of your chest, abdomen, and pelvis. MRI can be done if clinically indicated.
  - Brain MRI scan with contrast, if clinically indicated.
  - PET/CT, if clinically indicated.
  - Nuclear bone scan, if clinically indicated.
- Lab blood and urine tests
  - Routine and urine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, and other organs are working well as well as tumor markers. Blood will be drawn from a vein with a needle. The total amount of blood we will draw for research in this study will be less than 650 mL (about 44 tablespoons).
  - Urine or Serum pregnancy test (within 7 days)

    If you are pregnant, you will not be able to take part in this study.

In this study, you will undergo a series of treatment cycles, each lasting 2 weeks.

Bintrafusp alfa will be given through intravenously (IV) over 60 minutes once every 2 weeks. Visits usually take about 4-6 hours but should take no longer than 5 hours.

- For the prevention of infusion-related adverse effects and possible allergic reactions you may receive a premedication of a steroid (prednisone and/ or dexamethasone), an antihistamine drug (Benadryl) and/ or an anti-inflammatory drug (e.g., acetaminophen or ibuprofen) before the first 2 infusions of bintrafusp alfa. Based on how your body reacts to the first 2 infusions, the study doctor will see if you will need to continue receiving these premedication drugs with all of your other infusions.
- You will also remain in clinic for 30 minutes to 2 hours after bintrafusp alfa for observation for at least the first 4 times after you receive bintrafusp alfa.
- Re-treatment with bintrafusp alfa: If you complete all 26 doses and follow-up imaging 6-12 weeks after you finish treatment, and then show a sign of disease progression, you may be allowed to receive same dose regimen of bintrafusp alfa. This retreatment will start after repeating the required lab tests. Research labs and imaging will be done every 6-12 weeks. You may continue re-treatment up to 26 doses.

The following tests will be done prior to every cycle, at the end of treatment, about 28 days after the end of treatment, and during long-term follow-up as directed by your study doctor:

- Physical examination, including weight and vital signs as well as a review and discussion with your provider of your symptoms, medications and your ability to perform your normal activities.
- Routine lab tests
- Repeat CT scans. Every 8 weeks and then every 3 months if your tumor has a partial and/or complete response to the study drug.
- EKG to check your heart (at the end of treatment, and about 30 days after the end of treatment)

Additional research testing

In addition to the tests that we will conduct to determine whether you are having side effects or if your tumor is responding to the study therapy, we will also collect samples from you for purposes of research only. The samples are being done to look at the effects of therapy on your immune system and markers of tumor activity.

The samples included for these studies include:

- Blood Samples: Blood samples will be collected for required research studies to learn more about how the study drugs affect your body, the cancer, and your immune system, and to check for levels of some of the study drugs in the body. Where feasible, blood samples will be collected at cycle 1 day 1, week 1, week 3, week 9, and at the end of treatment (and/or at restaging if required; total ~9 tablespoons per visit when blood collected).
- Tumor Tissue and Biopsies: A portion of the biopsies done in the past for your cancer will be collected and are required. We may ask you to undergo three optional CT guided tumor biopsies for research at the following times: Day 1 of cycle 1 (within 1 week prior to first treatment), within 1 week of first imaging restaging and third one if your disease gets

worse. The biopsies are being collected for special research tests. You will be given an opportunity to decide at the time of each procedure. You may agree to biopsies now and change your mind later. If at any time you do not want to have a biopsy done, please tell us.

- Usually tissue can be obtained safely and comfortably with local anesthesia. If you require sedation before undergoing a biopsy, you will be informed of the risks and you will be asked to sign an additional consent prior to undergoing the procedure. Biopsies will NOT be done on this study if they require general anesthesia. We may ask that you have ultrasound/endoscopy to help clearly locate your tumor when doing a biopsy.

All of your samples collected for research purposes on this study (such as the tumor and normal tissue) may be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow.

To look at your DNA, we may use do what is called "whole genome sequencing." This where we will do special tests in the lab to look at the entire sequence, or order, of how your DNA is put together. This is what makes you unique.

To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and looking in detail at the parts of the genes that produce specific proteins.

However, you should know that the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described later in this consent form in the section for "**Return of research results**."

End of treatment visit

When you stop taking the study drug for any reasons, you will be asked to return to the clinic for the end of treatment visit. This end of treatment visit should occur within 14 days after you stop taking the study drug and, if possible, prior to starting any new therapy for your cancer.

At this visit, the study doctor/study team will do the following:

- Perform a complete physical examination;

- Record your vital signs (blood pressure, heart rate, body temperature, and breathing rate) and body weight;
- EKG;
- Blood sample collection; and,

Long-term follow-up visits

When you are finished taking the experimental therapy, we will ask you to come to the clinic for a safety visit (28 days post last dose). You will have follow-up visits and assessments at about every 3 months for the first year, then every 6 months for years 2-5, and then annually after that to monitor your disease status. These clinic visits may include CT (or MRI if clinically indicated) scans. It is preferred that you come to the clinic for your follow-up visits, but if not possible follow-up may be done by phone or email.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, you will receive bintrafusp for about one year and you will be followed annually as described above, for the rest of your life.

Your participation may end early if you decide to no longer take part in the study or your study doctor decides it is no longer suitable for you to continue.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 32 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

If you choose to take part in this study, there is a risk that the study drug may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.

- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Risks of the Study Drug

Bintrafusp alfa (M7824)

COMMON, SOME MAY BE SERIOUS In 100 people receiving bintrafusp alfa, more than 5 and up to 100 may have:
• Fatigue (tiredness and lack of energy) • Nausea • Diarrhea • Constipation • Vomiting • Swelling of your lower legs or hands • Fever • Decreased appetite • Loss of body fluids (dehydration) • Skin growths called keratoacanthomas that resemble skin cancer. These usually go away after treatment and can leave a scar. • Bleeding has been frequently observed in patients receiving bintrafusp alfa. Patients may experience bleeding in different organs such as gums, nose, ears, eyes, vagina, breasts, blood in their urine, stool, or bleeding in the internal organs or skull, coughing up or vomiting blood. Occasionally, this bleeding can be serious and potentially life threatening and require you to receive a blood transfusion. If you experience any bleeding on this trial, please tell the study team immediately. Tell your doctor if you've had a life-long problem of frequent or excessive bleeding or bruising, or if you take aspirin or prescription medication to thin your blood. • Shortness of breath • Cough • Anemia: low number of red blood cells that can cause tiredness and shortness of

breath. May require a blood transfusion.
- Abdominal pain
- Headache
- Itching

RARE
In 100 people receiving bintrafusp alfa, 5 or fewer may have:

- Chills (feeling cold)
- Blood clots that form throughout the body, blocking small blood vessels. Symptoms may include chest pain, shortness of breath, leg pain, problems speaking, or problems moving parts of the body.
- Easy bruising
- Reaction to other drugs such as rash, anaphylaxis, and changes in blood.
- Infusion-related reaction, including dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.
- Back pain
- Cancerous growth on the skin that can be removed
- Stroke
- Slow wound healing
- Thickening of the skin, nails.

In addition to the above, we have seen a few cases of nodular regenerative hyperplasia. This is when small growths, or nodules, occur in the liver. These usually do not cause symptoms, but can occasionally be associated with high blood pressure in the vein to the liver which could over time lead to liver damage.

Allergic reactions or reactions in the context with the infusions might occur during study treatment. Although bintrafusp alfa is a fully human protein the risk cannot be completely excluded In general, these reactions are mild to moderate and can be handled with appropriate drugs, but in very rare cases severe to life-threatening and even fatal reactions might occur, which require advanced cardiac life support.

Because of tumor shrinkage there is a risk of tumor lysis syndrome, a life-threatening condition. This complication is caused by the breakdown products of dying cells and includes elevated blood potassium, elevated blood phosphorus, elevated blood uric acid and elevated urine uric acid, low blood calcium, and consequent acute kidney failure. Signs of tumor lysis syndrome may include nausea, vomiting, decreased urination, muscle cramps/twitches or extreme fatigue.

In addition, immune-related side effects might be possible. These adverse events are caused by over activity of your body's immune system. The immune system normally protects you from

things that are harmful; such as infections, foreign substances, and sometimes from cancer. If the immune system is overactive, it can attack normal parts of the body because it mistakenly recognizes them as foreign/harmful.

Examples of these side effects are listed below. In rare cases, immune-related side effects can be life-threatening or fatal.

Types of immune related side effects:

- Inflammation in the lungs (pneumonitis): symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients: tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.
- Hypothyroidism (decreased function of the thyroid gland)
- Hyperthyroidism (increased function of thyroid gland)
- Thyroiditis (inflammatory disease of the thyroid gland)
- You may develop inflammation of the liver called hepatitis. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal.
- Thrombocytopenia (decrease of the blood platelets)
- Uveitis (inflammation in the eye)
- Diabetes mellitus (high blood sugar levels)
- Problems with your adrenal glands (Adrenal Insufficiency): May cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement.
- Myositis (inflammation of the muscles characterized by pain and tenderness)
- Inflammation of the intestine (colitis): It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening.
- Autoimmune encephalitis is a type of brain inflammation where the body's immune system attacks healthy cells and tissues in the brain or spinal cord.
- Myocarditis (inflammation of the heart muscle)
- Pemphigoid (fluid-filled blisters that can be itchy)
- Kidney problems: you may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by

inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement.

- Pancreatitis (inflammation of the pancreas)
- Liver problems: Increases in the blood level of substances called enzymes found within your liver cells. The enzyme changes are unlikely to make you feel unwell, however, if these blood enzyme levels become very high, your study doctor may need to stop the study medication.
- Nervous system problems: symptoms can include unusual weakness of legs, arms, or face, numbness, or tingling in hands or feet. In rare situations, there is the potential for the inflammation of the nervous system to be severe.

If any of these side effects occur, you must inform your study doctor immediately.

Risks of Study Procedures

Blood Collection

Risks of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Tumor Biopsy

If your doctor determines it is safe, we will obtain a piece of your tumor (biopsy) using a needle with minimal risk to you. You will be given local anesthesia (numbing medicine) and a sedative prior to the biopsy. The biopsy will be taken through a needle put through the skin into your tumor. Depending upon the location of your tumor, a CT scan may be used to assist the biopsy. After the procedure the nurses will watch your blood pressure and other vital signs.

There may be some temporary pain or discomfort during the procedure and afterwards in the area where the tissue was removed. You may also experience some bruising around the biopsy site over the following days. In rare cases an infection or bleeding may occur. Your doctor will give you a separate surgical consent form for this hospital procedure.

CT Scans and Contrast Dye

CT scans may be used to monitor your disease while you are in this study. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures showing the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan and you will be instructed to hold your breath. The scan itself will only take a few minutes to complete. CT scans expose you to radiation; the amount depends on the number of body areas scanned.

There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the test to confirm that it is safe you to receive the contrast.

If contrast is administered intravenously (IV), you may feel discomfort when the intravenous contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach.

MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

MRI Contrast Agents

During part of the MRI, people receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis (NSF)”. This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with

gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

EKG

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from up to 7 CT scans of the chest, abdomen and pelvis, up to 3 PET/CT scans, up to 2 bone scans and up to 3 CT-guided biopsies. The maximum amount of radiation exposure from these procedures is equal to approximately 14.28 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The radiation exposure that you may get in this study will expose you to the roughly the same amount of radiation as 47.6 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.4 out of 100 (1.4%). The risk of getting a fatal cancer is 0.7 out of 100 (0.7%).

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 65 days for women after you finish study treatment (the restricted period). For men, you will need to continue to practice an effective form of birth control for 125 days after you finish the study treatment. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact the study team as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study. However, the potential benefit to you might be shrinking of your tumor or decrease in your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because what we learn in this study may eventually be used to treat others with your disease.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with surgery, radiation or with drugs already approved by the FDA for your disease
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic Healthcare Provider to discuss the results.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you become pregnant

- if bintrafusp alfa becomes unavailable
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if the study is stopped for any reason

In this case, you will be informed of the reason therapy is being stopped.

After therapy is stopped, we would like to see you for a safety visit 28 days after your last dose.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to [redacted] or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will Your Specimens or Data Be Saved for Use in Other Research Studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding olfactory neuroblastoma, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will Your Specimens or Data Be Shared for Use in Other Research Studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

Will Your Genomic Data Be Shared Outside of This Study?

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive compensation for participation in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g. flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using bintrafusp alfa (M7824) drug developed by [redacted] through a joint study with your study team and the company. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, Center for Cancer Research (CCR), or their agent(s)
- Qualified representatives from [redacted], the pharmaceutical company who produces bintrafusp alfa.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Charalampos Floudas at [redacted] or [redacted]. You may also call the NIH Clinical Center Patient Representative at [redacted], or the NIH Office of IRB Operations at [redacted], if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.