THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Pilot, non-randomized, open-label study of intralesional nivolumab for high risk oral premalignant lesions
2021-1011

Study Chair: Moran Amit

_____ _____
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.

This research has been reviewed and approved by an Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

The goal of this clinical research study is to find the highest tolerable dose of nivolumab that can be given to patients with oral precancerous lesions.

Normally, nivolumab is given by vein (IV). However, in this study, nivolumab will be given as an injection directly into an oral lesion. Another goal of this study is to learn about the safety and possible side effects of giving nivolumab this way.

This is an investigational study. Nivolumab is FDA approved and commercially available for the treatment of many different types of cancer when given by vein, but it is not approved for the treatment of precancerous oral lesions. In this study, it is considered investigational to inject this drug directly into oral precancerous lesions.

The study doctor can explain how the study drug is designed to work.

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

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. If you take part in this study, you may experience side effects.

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

You may receive nivolumab every 3 weeks for up to 10 weeks.

Nivolumab will be provided at no cost to you while you are on study.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard treatments (observation or surgical removal of the disease) without taking part in this study. The study doctor will discuss the possible risks and benefits of these treatments. 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 quality medical care, including treatment for pain and other symptoms of cancer or pre-cancerous lesions.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. The following tests will be performed within 28 days before the first dose of study drug to help the study doctor decide if you are eligible:

- You will have a physical exam, including an oral exam.
- Blood (about 7 teaspoons) and urine will be collected for routine tests. Part of the blood sample will also be used to check for HIV and hepatitis B and C.
- You will have a chest x-ray to check the status of your lungs.
- You will have an EKG to check your heart function.
- You will have 2 punch biopsies from the precancerous lesion for biomarker testing (including genetic biomarkers) and immune system testing. Biomarkers are found in the blood/tissue and may help researchers understand your reaction to the study drug. To collect a punch biopsy, the area of biopsy is numbed with anesthetic and a small cut is made to remove all or part of the affected tissue.
- Photographs will be taken of your lesions. To protect your privacy, a picture of your face will not be taken. These pictures will be compared to pictures taken later in the study to learn how the lesions responded to the study drug.
- You will complete a questionnaire about your quality of life. It should take about 10-15 minutes to complete.
- If you can become pregnant, blood (about 1 teaspoon) will be drawn for pregnancy testing about 72 hours before your first dose. To take part in this study, you must not be pregnant.

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

Tissue Collection (LAB08-0848)
You will be given a separate consent form for another research study, LAB08-0848. As part of LAB08-0848, leftover tumor tissue from a previous procedure or future standard of care procedure may be collected to confirm your diagnosis and/or for future research. In addition to collection of leftover tissue, you will have tumor biopsies done as part of LAB08-0848. The separate consent form will explain this research to you in more detail, including how samples will be collected and any risks.

You must agree to take part in LAB08-0848 in order to take part in this study. The study staff will discuss this with you.

Study Groups
If you are found to be eligible to take part in this study, you will be assigned to a dose level of nivolumab based on when you join the study.

Up to 2 dose levels of nivolumab will be studied. Up to 12 participants will be enrolled in each dose level. The first group of participants will receive the lowest dose level of nivolumab. Each new group will receive a higher dose of nivolumab than the group before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of nivolumab is found.

Up to 31 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration
You will receive nivolumab as an injection directly into a precancerous lesion in your mouth on Day 1 of each 21-day study cycle for up to 4 cycles. If you have multiple lesions, only one lesion will receive an injection.

You will no longer be able to take the study drug if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions. Your participation will be over after the follow-up visits.

Study Visits

On **Day 1:**
- You will have a physical exam, including an oral exam.
- Blood (up to 3½ tablespoons) will be drawn for routine tests and research tests, including:
    - Circulating tumor DNA (ctDNA) testing—a measure of how much cancer is in the blood
    - Cytokine testing—types of proteins that may affect the immune system
    - Immune system and antibody testing— Antibodies are created by the

immune system and may attack foreign cells or substances, such as the study drug.
  - Genomic testing—A type of testing that helps researchers check for any mutations (changes) in your DNA (genetic information)
  - Tests to help researchers understand how your body is reacting to the study drug
  - Pharmacokinetic (PK) testing—Testing that measures how much study drug is in the blood at different time points. For this testing, blood will be drawn before and 2 times over the 48 hours after the dose of study drug.

On **Days 2 and 4:**
- Blood (about 3 teaspoons) will be drawn for PK testing.
- You will complete a quality of life questionnaire (Day 4 only).

On **Days 22, 43, and 64:**
- You will have a physical exam.
- Blood (up to 3½ tablespoons) will be drawn for routine and research tests.
- Photographs will be taken of lesions in your mouth.
- You will complete a quality of life questionnaire.
- If you can become pregnant, urine will be collected for a pregnancy test.

End-of-Study Visit

On **Day 85**:
- You will have a physical exam
- Blood (about 3½-5½ teaspoons) will be drawn for routine and research tests.
- Photographs will be taken of the oral lesions.
- You will complete the quality of life questionnaire.
- If you can become pregnant, urine will be collected for a pregnancy test.

Follow-Up Visits

On **Day 108 and 168:**
- You will have a physical exam.
- Blood (about 3½-5½ teaspoons) will be drawn for routine and research testing.
- You will complete the quality of life questionnaire.
- If you can become pregnant, urine will be collected for a pregnancy test.
- On Day 168, you will have the following additional tests:
  - You will have 2 punch biopsies for research testing.
  - You will have an EKG.

Early Stopping

If you stop taking the study drug before Day 85, you will have the End-of-Study Visit as soon as possible after the drug is stopped. After that, you will have the above follow-up visits about 30 and 90 days after that.

Other Information

Tell your study doctor about any other drugs you are taking while on study. This includes prescription drugs, over-the-counter medications, vitamins, nutritional supplements, herbal medications, and alternative treatments.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. 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.

Side effects will vary from person to person, and some may occur after you have stopped receiving treatment. Tell the study staff about any side effects you may have, even if you do not think they are related to the study drug/procedure.

Nivolumab Side Effects

The following side effects have been seen when nivolumab is given as an infusion (by vein).

Common (occurring in more than 10%)

• fatigue/lack of energy	• diarrhea • itching	• skin rash

Occasional (occurring in 3-10%)

• fever • underactive thyroid gland (possible increased thyroid stimulating hormone lab test result, weight gain, heart failure, and/or constipation)	• abnormal digestive blood test (possible inflammation of the pancreas) • nausea/vomiting • abdominal pain • loss of appetite • low red blood cell count	• abnormal liver test (possible liver damage and/or yellowing of the eyes and/or skin) • pain (including muscle/bone) • lung inflammation (pneumonitis), and/or bronchitis (possible difficulty breathing)

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

Rare (occurring in fewer than 3% of patients)

• fast heartbeat • abnormal EKG • heart inflammation/ inflammation of the tissue around the heart (possible chest pain) • high blood pressure • low blood pressure (possible dizziness and/or fainting) • swelling of the brain (possible headache and/or mental status changes) • inflammation of the brain and spinal cord (possible altered consciousness) • inflammation of the membrane around the spinal cord and brain (possible headache and/or coma) • swelling (face/arms/legs) • chills • headache • difficulty sleeping • dizziness • dry/red skin • hives • skin blisters • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract) • red, dry, scaly patches of thickened skin (psoriasis) • allergic skin reaction	• decreased production of adrenal hormones (possible weakness and/or low blood pressure) • inflammation of the thyroid gland (possible tenderness in the neck) • pituitary gland failure (possible hormone imbalance) • blood vessel inflammation • low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • abnormal blood test (possible pancreas damage) • high blood sugar (possible diabetes) • diabetes • abnormal blood acid/base balance due to uncontrolled diabetes (possible organ damage) • mouth blisters/sores (possible difficulty swallowing) • constipation • dehydration • dry mouth • inflammation of the intestines • hole in the intestines (possibly leaking contents into the abdomen) • liver inflammation • liver failure/damage	• abnormal kidney test (possible kidney damage) • kidney failure • breakdown of muscle tissue (possible kidney failure) • damage to the nervous system (causing numbness and/or paralysis) • nerve damage (possible numbness, pain, and/or loss of motor function and/or “pins and needles” sensation) • nerve damage (affecting the head and neck) • muscle inflammation • joint pain/stiffness • dry eye • blurry/double vision • difficulty breathing • cough • infusion reaction (possible fever, rash, pain, and/or swelling) • immune response causing the body to attack itself (possibly causing muscle weakness) • immune system reaction (possible fever, jaundice, liver/spleen enlargement, irritability, and/or seizures) • multi-organ disease causing lesions, most

• hair loss (partial or total) • overactive thyroid gland (possible decreased thyroid stimulating hormone lab test result, weight loss, heart rate changes, and/or sweating)	• low blood cell count (platelets, white) • destruction of red blood cells due to the body attacking itself (called autoimmune hemolytic anemia)	often in the lungs (sarcoidosis) • allergic reaction, possibly life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure) • patches of skin color loss • inflammation of multiple areas of the body (see below)

You may need to take drugs to reduce inflammation while taking nivolumab. Long-term use of these drugs may increase your risk of infection. These infections may occur anywhere and may be fatal. Treatment with antibiotic or antifungal drugs may be required to treat these infections.

The study drug works by boosting the immune system. This may cause unknown side effects resulting from your immune system attacking your organs. This may cause inflammation and inflammation-related side effects in any organ or tissue.

Nivolumab may cause serious side effects that affect your immune system. Some of these side effects start as inflammation in different areas of the body like the skin, hormone glands, pancreas, eye, kidney, or stomach. Tell the study staff right away if you have diarrhea, nausea, vomiting, blurred vision, dizziness, fainting, or you are feeling cold all the time.

Nivolumab may rarely cause low blood cell counts (platelets and/or white blood cells):

- A low platelet count (thrombocytopenia) increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count (neutropenia) 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.

Frequency Unknown

• graft-versus-host disease (when transplanted donor tissue attacks the tissues of the recipient's body) • Hemophagocytic lymphohistiocytosis (HLH) syndrome (see below)	• Vogt Koyanagi Harada syndrome -- pigmented tissue (possible eye pain/swelling, hearing loss, and/or loss of skin color) • risk of organ transplant rejection

Nivolumab may cause Hemophagocytic lymphohistiocytosis (HLH) syndrome at an unknown frequency. HLH is a disease that may affect your body's defense system, (your immune system) and certain white blood cells made by your immune system

may attack other blood cells. These abnormal blood cells collect in your spleen and liver, causing these organs to enlarge, possibly causing fever, rash, and low blood cell counts.

Other Risks

Receiving nivolumab as an injection into the mouth may be painful and/or uncomfortable. The area may need to be numbed before the injection.

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.

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

EKGs may cause discomfort while lying on the exam table, and the tape on the EKG pads may cause skin irritation.

X-rays send a small amount of radiation though the body. All radiation adds up over a lifetime and may increase the risk of a new cancer forming.

Digital photographs of lesions taken during the study will be temporarily stored at MD Anderson in a secured computer that will be used only for this study. The study staff will upload the images through a secured website for central review. In case of any issues with this uploading method, MD Anderson may send the images by using a USB flash drive (a portable storage device that will be used only for the purpose of the study) and ship the drive using secure and approved shipment methods. In all instances and to ensure your privacy, your name and any other identifying information will not be attached to your images, you will only be identified by the subject number. At all times appropriate secure control measures are taken to ensure your privacy and only authorized personnel will have access to your images.

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.

Samples collected from you as part of this study will be used for **genetic research**, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you.

A federal law, called the **Genetic Information Nondiscrimination Act (GINA)**, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

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, which may result in a **loss of confidentiality**. 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.

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.

If you are sexually active, you must use 2 medically acceptable methods of birth control from the start of the study and until 120 days after your last dose of study drug. You may choose to use 2 barrier methods or a barrier method plus a hormonal birth control method.

Acceptable barrier methods include diaphragm, condom, or sponge with spermicide. Acceptable hormonal methods include birth control pills, patches, intrauterine device (IUD), or injections that contain estrogen and/or progestogen.

Tell the doctor right away if you/your partner becomes pregnant or suspects pregnancy.

If you are female and you are pregnant, you will not be enrolled on this study. Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, leftover samples (blood/tissue) and your personal information will be stored at MD Anderson and used by researchers at MD Anderson for use in future research related to cancer and/or other diseases. Your data/samples may be shared with other researchers and/or institutions as part of this future research.

Before being shared for future research, every effort will be made to remove your identifying information from any data. 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 and/or samples are used for future research. If this research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data/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.

You do not have to agree to the optional procedure in order to take part in this study. There are no benefits to you for taking part in the optional procedure. 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 procedure.

Optional Procedure Risks

Researchers 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 by researchers under the supervision of the study chair.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

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

Optional Procedure #1: Do you agree to allow MD Anderson to use your personal information and/or research samples for future research related to cancer and/or other diseases?

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 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. Moran Amit, at 713-794-5304) 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 who can help you safely stop study treatment. It may be dangerous to suddenly stop study treatment. The study doctor will also decide if you need to have any visits or tests to check on your health. If you withdraw from this study, you can still choose to be treated at MD Anderson.

If you stop being in the research, already collected data may not be removed from the study database. You may be asked whether the study doctor can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

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. Possible reasons your participation in this study may be stopped include if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

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

   You will receive the results of your screening biopsy and research blood tests.

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

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
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form

   Samples collected from you during this study will be stored in a secure storage space at MD Anderson for up to 15 years after the completion of the study for the research purposes described in this consent form, unless you withdraw your consent to store your samples. If you wish to withdraw your

consent to use and store your samples, please tell the study doctor in writing.

To protect your identity, the samples collected from you will be labeled a unique number instead of your name or other identifying information. Only the study doctor or study staff will have access to the code that can link you to your samples.

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

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under this protocol.

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

A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS) and patients who are illiterate.

_____
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