THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

TITLE:	A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Advanced Rare Cancers (SiARa Cancer Study) – Cancer of Unknown Primary (SiARa-CUP)
PROTOCOL NO.:	2020-0902 IRB Protocol #20210011
SPONSOR:	UT MD Anderson Cancer Center and Innovent Inc.
INVESTIGATOR:	Kanwal Raghav, MBBS, MD 1515 Holcombe Blvd Houston, Texas 77030 United States
STUDY-RELATED PHONE NUMBER(S):	713-792-2828 713-792-2121 (24-hours)

_____ _____
Participant's Name Medical Record Number

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

STUDY SUMMARY

The goal of this clinical research study is to learn if sintilimab can help to control the disease in patients with cancers of an unknown primary (the place on the body where the cancer began is not known). The safety and effects of sintilimab will also be studied.

This is an investigational study. The use of Sintilimab in this study is investigational and is not U.S. Food and Drug Administration (FDA) approved or commercially available. Its use in this study is for research purposes only. The study doctor can explain how the study drug is designed to work.

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

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. If you are from outside the Houston area, taking part in this study may require a prolonged stay out of town.

You can read a list of potential side effects below in the Possible Risks section of this consent. In addition to common sides associated with other cancer drugs, other risks you should be aware include the possibility of tumor pseudoprogression, low red blood cell counts, and boosting of the immune system. A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion. Boosting the immune system 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.

You may receive the study drug for up to 2 years.

The most important procedures to be followed in this research are the skin biopsy along with local and general anesthesia. These are discussed in the procedures and risk sections.

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

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive other standard procedures or treatment options. 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 be provided appropriate medical care, including treatment for pain and other symptoms of cancer.

If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

STUDY DETAILS

Screening Tests

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

- You will have a physical exam.
- You will have an EKG to check your heart function. This EKG will be performed within 7 days before your first dose.

- Blood (about 1 tablespoon) will be drawn for the following tests:
  - Routine tests
  - Tests to check your thyroid function
  - Pharmacokinetic (PK) testing – PK testing measures the amount of study drug in the body at different time points
  - Antibody testing – antibodies are created by the immune system and may attack foreign cells or substances, such as the study drug
  - Tests to check for hepatitis B and C and HIV (the AIDS virus). If you test positive for hepatitis or HIV, the test results and your name, address, date of birth, and sex will be shared with appropriate health authorities as required by law. You will also be given a list of places in your area so that you can receive further testing and treatment.
  - If you can become pregnant, part of this sample will be used for a pregnancy test. To take part in this study, you must not be pregnant. This pregnancy test will be performed within 3 days before your first dose.
- Urine will be collected for routine tests.
- You will have imaging scans (such as a CT scan, MRI, and/or PET scan) to check the status of the disease. The type of imaging scans you have will be consistent throughout this study.
- Archival (leftover) tissue from a previous procedure will be collected for biomarker testing. Biomarkers are found in the blood/tissue and may be related to the status of the disease. If no leftover tissue is available, you will have a core needle or excisional biopsy. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge. To perform an excisional biopsy, the affected area is completely removed by cutting it out.

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

Up to 45 participants will take part in this study. All will be enrolled at MD Anderson.

Study Drug Administration
Each cycle is 21 days (3 weeks).

You will receive sintilimab by vein over about 1 hour on Day 1 of each cycle for up to 2 years. If you tolerate the study drug well, you may be able to receive the study drug over 30 minutes in Cycles 2 and beyond.

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

Your participation in this study will be over after the follow-up visits.

Study Visits

On **Day 1 of Cycle 1:**

- You will have a physical exam.
- Blood (about 1 ½ tablespoons) will be drawn for routine, biomarker, PK, and antibody testing. A PK sample will be drawn before the dose and any time between 2-24 hours after the dose.
- Urine will be collected for routine tests.
- You will complete questionnaires about your symptoms and quality of life. These questionnaires should take about 5-10 minutes to complete.

On **Day 8 of Cycle 1,** blood (about 2 teaspoons) will be drawn for biomarker and PK testing.

On **Day 1 of Cycles 2 and beyond:**

- You will have a physical exam.
- You will have an EKG to check your heart function.
- Blood (about 1 ½ tablespoons) will be drawn for routine, PK, antibody, biomarker, and PK testing. A part of the sample will also be used to check your thyroid function.
- Urine will be collected for routine tests. During even cycles only, if you can become pregnant, this sample will also be used collected for a pregnancy test. If the urine test is not conclusive, a blood pregnancy test will also be performed.
- You will complete questionnaires about your symptoms and quality of life.
- During Cycle 2 only, you will have a tumor biopsy to check the status of the disease.

Every 9 weeks throughout this study, you will have imaging scans to check the status of the disease.

End-of-Treatment Visit

Within 7 days after your last dose, you will have an End-of-Treatment Visit. The following tests and procedures will be performed at this visit:

- You will have a physical exam.
- You will have an EKG to check your heart function.
- Blood (about 1 ½ tablespoons) will be drawn for routine, PK, antibody, and biomarker testing. A part of this sample will also be used to check your thyroid function.
- Urine will be collected for routine tests. If you can become pregnant, part of this sample will also be used for a pregnancy test. If the urine test is not conclusive, you will also have a blood pregnancy test.
- You will complete the questionnaires about your quality of life and symptoms.
- You will have imaging scans to check the status of the disease.

Safety Follow-Up Visits

About 30 days after your last dose or before you start a new anti-cancer therapy, you will have a safety follow-up visit. If it has been less than 7 days since your End-of-Treatment Visit, this visit may not be needed. The following tests and procedures will be performed:

- You will have an EKG to check your heart function.
- Blood (about 2 teaspoons) will be drawn for routine, PK, and antibody testing.
- Urine will be collected for routine tests.
- You will complete the questionnaires about your quality of life and symptoms.

About 90 days after your last dose, the study staff will call you to check on how you are doing, any symptoms you have, and any anti-cancer treatments you have started. The phone call should take about 15-20 minutes.

Long-Term Follow-Up

Every 60 days after your safety follow-up visits, the study staff will call you to check on how you are doing and any new anti-cancer treatments you have started. This phone call should take about 15 minutes.

If you stopped taking the study drug for reasons other than the disease getting worse, **every 12 weeks until the end of the study, you start a new anti-cancer treatment, or the disease gets worse**, you will have imaging scans to check the status of the disease.

POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. 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. 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 drugs/procedures.

Sintilimab Side Effects

This is an early study of sintilimab in humans, so the side effects are not well known. Based on similar drugs, sintilimab may cause the following side effects:

• slow/irregular/fast heartbeat • high blood pressure	• underactive thyroid gland (possible weight gain, heart failure, and/or constipation)	• high blood levels of fat (possible heart disease and/or stroke)

• abnormal EKG • chest pain • heart failure • heart inflammation • fever • dizziness • difficulty sleeping • nervous system damage • facial nerve disorder • weakness • fatigue • chills • hives • pain (joint/limb) • skin rash • eczema (skin inflammation) • dry skin • itching • patches of skin color loss • abnormal growth in the thyroid • enlarged thyroid gland with neck swelling • elevated hormone levels • 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 thyroid gland (possible tenderness in the neck) • loss of appetite • weight loss or gain • mouth blisters/sores • vomiting/nausea • diarrhea • constipation • digestive system bleeding • inflammation of intestine • high blood levels of uric acid (possible painful joints and/or kidney failure) • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• diabetes • high blood sugar (possible diabetes) • severe high blood sugar due to uncontrolled diabetes • low red blood cell count • abnormal liver tests (possible liver damage) • abnormal liver function • liver damage • abnormal kidney tests (possible kidney damage) • kidney damage and/or inflammation • blood in urine • lung inflammation (possible difficulty breathing) • cough • difficulty breathing • infection • infusion reaction (possible chills/hives) • allergic reaction

Sintilimab may cause tumor pseudoprogression. This occurs when the number and/or size of tumor(s) appear to increase in imaging scans. In reality, it is usually an inflammatory response with swelling that makes your tumors appear to be larger.

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

Sintilimab 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.

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.

EKG

You may have skin irritation from the contacts used.

Biopsy

The risks of a biopsy depend on the location of tissue in your body being biopsied, the organs at and near that location, and the procedure the doctors need to use to get to that location. A biopsy may be as simple and quick like a needle stick for a blood draw, or may require surgery and general anesthesia to get access to the organ being biopsied. Therefore, depending on the specifics of the biopsy, the side effects may range from brief mild pain to serious bleeding, infection, or organ damage. Before you decide to take part in this research the research team will make sure you are informed of the risks of the biopsy that is specific to your situation.

Local anesthesia

Local anesthesia can cause temporary discomfort, allergic reaction, bruising or bleeding.

General anesthesia

The common side effects of general anesthesia include nausea and vomiting, dry mouth, sore throat or hoarseness, chills, confusion, dizziness, muscle aches, itching and difficulty urinating. Serious, life threatening side effects such as heart rhythm disturbances, strokes or accidents causing brain damage can occur.

CT With Contrast

This test will expose you to radiation.

Oral contrast: Risks include nausea.

IV contrasts: The tests in this study may include contrast dyes, which may cause infusion reactions and rarely cause serious reactions, such as life-threatening allergic reactions or kidney damage.

PET

Pain, bleeding, bruising, or fainting from injection of a radioactive substance into a vein. The scan will expose you to radiation.

MRI:

Contrast dye may be used, which has a small possibility of a severe allergic reaction and may also cause kidney problems, especially if you are dehydrated or have poor kidney function.

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.

There is the risk of loss of confidentiality.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Taking part in this study can result in unknown 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 and for 180 days after your last dose of study drug if you are sexually active.

Birth Control Specifications: You must use either 1 single-method birth control option or 2 double barrier birth control options during this study and for 180 days after your last dose of study drug.

Single-method birth control options include 1) an intrauterine device ("IUD") or 2) a birth control implant.

Double barrier birth control options include: 1) condoms, 2) a diaphragm/cervical cap with spermicide, and/or 3) a hormonal birth control method such as birth control pills, patch, or ring.

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

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away. You will be asked to provide follow up information on your pregnancy and its outcome.

Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

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

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
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.

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 if the disease gets worse?

YES **NO**

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. There are no plans made by MD Anderson or Innovent to reimburse you for expenses or to compensate you financially for this injury.

If you suffer a study-related injury, you may contact the Chair of the study, Dr. Kanwal P. Raghav, at 713-792-2828, or 713-792-2121 (24-hours) with any questions you may have. 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 billed 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. Commercial profit from products developed from your bio-specimens will not be shared with you.

Future research which may result in clinically relevant findings will not be disclosed to you.

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

You may ask the study chair any questions you have about this study, if you have any questions, concerns, or complaints about the research, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug. You may contact the study chair, Dr. Kanwal P. Raghav, at 713-792-2828, or 713-792-2121 (24-hours).

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

WCG IRB
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 855-818-2289
E-mail: researchquestions@wcgirb.com

WCGIRB is a group of people who perform independent review of research.

WCGIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WCGIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

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 to which you are otherwise entitled.

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.

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

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.

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

This study is sponsored and/or supported by: Innovent.

In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s). If you have any questions about this, you may call WCGIRB at 1-800-562-4789.

The MD Anderson Conflict of Interest (COI) policy states that MD Anderson employees may not serve as the study chair or co-chair on a research study if they have received funds that are greater than the amount allowed by the policy or own stock in the sponsoring or supporting companies.

The COI policy and the IRB require that you be told about financial relationships that the study investigators may have with the study sponsor(s).

The MD Anderson Institutional Conflict of Interest policy requires that you be told about financial relationships that MD Anderson Institutional Decision Makers may have with the study sponsor(s) and significant financial relationships that MD Anderson may have with the study sponsor(s).

The terms of MD Anderson's agreement with Innovent have been identified as creating both a Significant Financial Interest and an Institutional Conflict of Interest by MD Anderson's Institutional Conflict of Interest Committee.

The results of this study may result in a financial benefit for MD Anderson.

MD Anderson has taken steps to manage this Institutional Conflict of Interest. The plan to manage the conflict has been approved by the Executive Vice Chancellor for Health Affairs for The University of Texas System.

This Institutional Conflict of Interest may affect your willingness to take part in this study. If you have any questions or concerns related to MD Anderson's Institutional Conflict of Interest with Innovent, please call the MD Anderson Institutional Compliance Office at 713-745-6636. That office will provide you the contact information for a non-MD Anderson ethicist who can assist with your questions and concerns. In the event, a non-MD Anderson ethicist is not available, an MD Anderson ethicist will contact you to assist with your questions and concerns.

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 Innovent and/or shared with other researchers and/or institutions for use in future research.

Samples

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

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

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

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

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

Authorization for Use and Disclosure of Protected Health Information:

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:

- Innovent (and/or any future sponsors of the study)
- The EVC and the Office of General Counsel for The University of Texas System
- Any future licensees of the study technology and an External Data Safety and Monitoring Board
- Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
- WCGIRB
- A non-MD Anderson ethicist
- 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. If the results of this research are published, you will not be identified.

If results from this study are published, such as in medical journals or online, your name and other identifying information will not be used.

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. If the results of this study are made public, information that identifies you will not be used.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI and it may be re-disclosed.

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 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 voluntarily agree to participate in this study. I authorize the release of my medical and research records for the purpose of this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed and dated copy of this consent document.

_____ _____

SIGNATURE OF PARTICIPANT DATE

_____

PRINTED NAME OF PARTICIPANT

PERSON OBTAINING CONSENT

I have discussed this clinical research study with the participant, 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