UMCC 2018.052

Multi-center Trial of ESK981 in Combination with Nivolumab in Patients With Metastatic Renal Cell Carcinoma

NCT03562507

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title:
ERICA: Phase 2 Multi-center Trial of ESK981 in Combination with Nivolumab in Patients With Metastatic Renal Cell Carcinoma

Company or agency sponsoring the study: The University of Michigan along with support from Esanik Therapeutics, Inc.

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):

Principal Investigator:
Ajjai Alva, MD Department of Internal Medicine, Hematology/Oncology, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains information that will help you decide whether to join the study. All information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your possible participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

As researchers have learned more about the changes in cells that cause cancer, they have developed newer drugs that target some of these cell changes. Targeted drugs are different from standard chemotherapy drugs and they sometimes work when standard chemotherapy drugs don't. Targeted drugs are proving to be especially important in kidney cancer, where traditional chemotherapy has not been shown to be very effective.
There are two parts to this study:

The first part of the study is to test the effectiveness (how well the drug works), safety, and tolerability of the investigational drug ESK981 alone in patients with advanced kidney cancer.

The second part of the study is to test the effectiveness (how well the drug works), safety, and tolerability of the investigational drug ESK981 when combined with an immunotherapy drug nivolumab in patients with advanced kidney cancer.

Nivolumab is an immunotherapy drug that has been approved by the Food and Drug Administration (FDA) for the treatment of kidney cancer, classical Hodgkin lymphoma that has relapsed or progressed, metastatic melanoma (a type of skin cancer), previously treated advanced colorectal, urinary tract, lung, head & neck and liver cancers.

ESK981 (formerly known as CEP-11981) is an investigational drug in this study because it has not been approved by the FDA for the treatment of kidney cancer or any cancers.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Adult men or women who have advanced kidney cancers.

There are many other inclusion and exclusion criteria (a sort of checklist) which the doctors will use to determine if you can participate in this study. It is important that you discuss your full medical history and all of your medications with your doctor.

3.2 How many people (subjects) are expected to take part in this study?

A total of approximately 50 subjects at several institutions will take part in this study, including approximately 30 subjects from the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

The study team will explain the research study and answer any questions you have about the study. If you want to participate in the study, the study team will request you sign this consent form prior to any activities occurring that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Many of the procedures that will be performed during the study, including routine blood tests, disease evaluations, physical examinations, vital signs (blood pressure, heart rate, breathing rate, and temperature) and measurement of height and weight, would normally be done as part of your standard of care regardless of study participation. However, some of these may be done more frequently as a result of your participation in this study. Tests and procedures that are done more often than your regular medical care because of your study participation and that are solely for research purposes will be identified below. The study staff will inform you of the types of tests and procedures you have to undergo during the study.

During the study you must:

- Follow the instructions you are given.
- Come to the study center for your visits with the study doctor.
- Tell the study doctor or study staff about any changes in your health and/or medications you are taking.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

Before starting the study: Some exams, tests, and procedures will be required to find out if you can be in this study. If you have had some of the tests recently, they may not need to be repeated. The screening tests and procedures do not have to be completed in one day and you are allowed to take breaks if you have multiple procedures in one day.

The following tests and procedures will be performed during screening and/or at one or more study visits. Refer to the study calendar below for information about which procedures will be performed at certain study visits.

- **Medical history**: including any past treatments, surgeries, infection and autoimmune diseases.

- **Medications**: It is important that you tell your doctor about all of the medications that you have been taking, including over the counter medicines, vitamins or herbal treatments.

- **Physical exam/Vital Signs**: including measurement of your height (screening only), weight, blood pressure, heart rate, respiratory rate and temperature.

- **Performance status**: Your ability to perform day to day activities and care for yourself

- **Routine blood tests (approximately 2 teaspoons)**: will be drawn for tests to check blood counts, chemistry, thyroid health and blood markers for cancer

- **Pregnancy test**: (urine or blood – approximately 1 teaspoon): if you are a woman able to have children

- **Scans of your cancer**: these could include Computed tomography (CT) of the chest, or CT or magnetic resonance imaging (MRI) of the upper and lower belly.
    - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.
    - A MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie down on a narrow bed which will slide into a tunnel that is 6 feet long by 22 inches across and is open at each end. You will be asked to lie quietly for about one hour, during which time you will hear a loud machine-like noise. A MRI scan takes about an hour and a half to complete.

- **Toxicity evaluation:** You will be asked about any side effects or illnesses you experience.

- **Tumor tissue:** Your doctor will check to see if you have enough stored tissue sample of your tumor that was collected previously. You may still participate in this clinical trial even if you do not have enough stored tissue. *This is for research purposes.*

- **Blood for Biomarkers (approximately 5-6 tablespoons):** Will be drawn for testing for biomarkers (testing of substances such as proteins that tell us how the drug is working in your body). *This is for research purposes.*

- **Questionnaire:** You will be asked to complete a quality of life questionnaire asking about your symptoms and how your disease and symptoms make you feel. You may find some of the questions uncomfortable to answer. You do not have to answer any question you do not want to answer. *This is for research purposes*.

Study Intervention (for Research):
If you qualify to participate in the study based on the results of the screening tests and procedures, you will return to the study doctor's clinic.

The researchers will tell you which part of the study you will be participating in and what drug or drugs you will be getting. There is no placebo or dummy drug in this study. Which part you participate in will depend on how far along we are in the study.

For this study a cycle is defined as 28 days.

Part 1:
If you participate in Part 1 of this study you will take ESK981 by mouth on days 1-5 of each week. You will not take ESK981 on days 6 and 7 of each week.

If you experience adverse events, you might have to stop taking ESK981 and if you recover from your adverse events, you may be able to restart the study drug.

You may continue to take ESK981 as long as you are tolerating the investigational study treatment and your disease has not progressed.

Part 2:
If you participate in Part 2 of this study, on day 1 of each cycle you will receive nivolumab intravenously (through a vein in your arm or port). You will also take ESK981 by mouth on days 1-5 of each week. You will not take ESK981 on days 6 and 7 of each week.

If you experience adverse events, you might have to stop taking ESK981 and/or nivolumab and if you recover from your adverse events, you may be able to restart the study drug(s).

You may continue to take ESK981 and receive nivolumab for as long as you are tolerating the investigational study treatment and your disease has not progressed.

The researchers will ask you to complete a drug diary to track what days you take ESK981. Please bring your drug diary and medication bottles (empty and/or with extra tablets) with you when you return for each appointment.

Below are general rules for taking ESK981:

- Take either with food or without food
- Swallow whole (do NOT chew, crush or cut the capsule)
- The medication SHOULD NOT be ingested if broken, cracked or otherwise not intact.
- If you miss a dose (i.e. you do not take it within 6 hours of the scheduled time) DO NOT “make it up”. Skip the missed dose and start taking ESK981 with the next scheduled dose.
- If you vomit any time after taking a dose DO NOT “make it up”.
- Store in the refrigerator

Follow-up:

If you stop the study intervention for any reason you will be asked to return for end of treatment visit 30 days after your last dose of study intervention.

After you complete the end of treatment you will have an office visit or be contacted by a member of the study team every 3 months for up to 2 years from when you stopped the study intervention.

See the table for a summary of the study intervention and procedures.

Study Procedures Table:
Each cycle is 28 days or 4 weeks

Procedures	Screening	Cycle 1 Day1	Cycle 2 Day 1	Cycle 3 Day1	Cycle 4 Day1	Day 1 of Cycle 5 and beyond	End of Treatment Visit	Follow Up
Medical History	X	X	X	X	X	X	X	
Medication Review	X	X	X	X	X	X	X	
Physical Exam/vital signs	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	
Pregnancy Test	X							
Routine Blood Tests	X	X*	X*	X	X	X	X	
Toxicity Evaluations	X	X	X	X	X	X	X	
Scans/Imaging of your cancer	X	Every 8 weeks for the first 4 assessments then every 12 weeks						X
Questionnaires		Cycles 1, 2, 3, 5, 7, 9 and then every 12 weeks						
Tumor tissue submission	X							
Research blood		X						
Survival Status								X Every 12 weeks

* Routine blood tests to check blood counts will be drawn weekly in Cycles 1 and 2. If you are tolerating the study intervention your routine blood tests to check blood counts will be drawn monthly after Cycle 2.

OPTIONAL Research Samples Stored for Unspecified Future Research:

Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your research blood and tumor tissue, as well as medical information (such as gender, race, and how your cancer responded to the study intervention, etc.) collected in the main study so that we may study them in future research. The future research may be similar to this study or may be completely different and may include genetic analysis on your tissue.

You can take part in the main study even if you decide not to let us keep your blood, tumor tissue and medical information for future research.

If you give us permission, we will use your blood, tumor tissue and medical information for future research. Even if you give us permission now to keep some of your blood, tissue and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your blood and tissue, we may not be able to take the information out of our research.

We may share your blood, tumor tissue and medical information with other researchers, so that they can use it in their research. Once we have shared your blood, tissue and medical information with other researchers, we will

not be able to get it back. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your blood and tumor tissue samples. Allowing us to do future research on your blood, tissue and medical information will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the future research on your blood, tumor tissue and medical information. You will not have rights to these discoveries or any proceeds from them.

You can make your choice about whether to participate in the Optional substudy (storage of research samples for future use) in Section 12 of the consent.

4.2 How much of my time will be needed to take part in this study?
The initial screening visit will take approximately 2-5 hours. Each study visit is expected to take approximately 4-6 hours.

4.3 When will my participation in the study be over?
The maximum time you will be in the study will depend on how your disease responds to the study intervention and how well you tolerate the study intervention. After you stop taking the study intervention you will be asked to come back for an end of treatment visit and then we will follow you either by phone or a clinic visit for up to 2 years. Your participation may end sooner if you decide to no longer participate, your study doctor feels it is in your best interest to stop your study participation, your disease progresses or the study is ended. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular physician first.

4.4 What will happen with my information and/or biospecimens used in this study?
Your collected information and biospecimens may be shared with Esanik Therapeutics, Inc. Your collected information and biospecimens may also be shared with other researchers, both here or around the world, or with companies. Any sharing is subject to contractual obligations with the Sponsor. Additionally:

- With appropriate permissions, your identifiable collected information and biospecimens may be shared, and/or,
- Without your additional consent, your identifiable private information and identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The drugs used in the study may cause certain side effects and discomforts. You may have all, some, or none of the known side effects. There is also a risk that other rare or unknown side effects may occur. Your doctors and nurses will check you closely for side effects, and may give you medicines or other treatments to stop or reduce some of these effects. Some side effects may go away soon after the study medication is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent. There is even a chance that a side effect may cause death. If you have any side effects, it is important that you report them to your study doctor or research staff.

These risks will be minimized by monitoring you carefully. We will provide the usual supportive care that would be routinely given to someone with your condition. If you have side effects from the study intervention, we will make appropriate adjustments as defined by the study protocol. You may need to discontinue the study intervention if the side effects are too serious.

The known or expected risks are:

Side Effects ASSOCIATED WITH ESK981

By taking part in this study, you may experience the following risks from the study drug ESK981:

Very frequent (greater than 50% or >1/2 patients):

- Fatigue

Frequent (20% to 50% or 1/5 to 1/2 patients):

- Nausea
- Diarrhea
- Decreased appetite
- Abdominal pain
- Back pain
- Vomiting
- Constipation
- Headache
- Dizziness
- Difficulty breathing (dyspnea)

Less Frequent (less than 20% or less than 1/5 patients):

- Reduced white blood cells, which can increase the risk of infection

Rare:

- Raised body temperature (pyrexia)
- Low red blood cells (hemolytic anemia), causing sever fatigue
- Liver failure (hyperbilirubinemia)
- Serious difficulty breathing (dyspnea)
- Severely low white blood cell counts (neutropenia), which may increase the risk of infections
- Changes in your heart activity (ECG (electrocardiogram) change)
- Chest discomfort

Side Effects ASSOCIATED WITH NIVOLUMAB

Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects that you experience.

Very common side effects of nivolumab (occurring in ≥ 10% or ≥ 1/10 of patients) are:

- Fatigue
- Rash
- Musculoskeletal pain
- Itchy skin
- Diarrhea
- Nausea
- Weakness
- Cough
- Shortness of breath
- Constipation
- Decreased appetite
- Back pain
- Joint pain or stiffness
- Upper respiratory tract infection
- Fever
- Headache
- Abdominal pain

Common side effects of nivolumab (occurring in ≥1% to 10% or ≥ 1/100 to 1/10 of patients):

- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
- ALT increased: lab test result associated with abnormal liver function
- Amylase increased: lab test result associated with pancreas inflammation
- AST increased: lab test result associated with abnormal liver function
- Chills
- Creatinine increased: lab test result associated with decreased kidney function
- Dry mouth
- Dry skin
- Lipase increased: lab test result associated with pancreas inflammation
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Itching
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis - see details below)
- Swelling, including face, arms, and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Thyroid stimulating hormone increased: lab test result associated with abnormal thyroid function

- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting

Uncommon side effects of nivolumab (occurring in ≥0.1% to 1% or ≥ 1/1,000 to < 1/100 of patients):

- Adrenal gland function decreased
- Allergic reaction
- Abnormal liver function blood test (bilirubin increased)
- Bronchitis
- Cranial nerve disorder
- Diabetes
- Dizziness
- Dry eye
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure
- Hives
- Increased blood sugar
- Inflammation of the eye
- Inflammation of the heart
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland
- Liver inflammation
- Low blood pressure
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Redness
- Kidney failure
- Respiratory failure
- Sodium levels in blood low
- Upper respiratory tract infection
- Vision blurred

Rare side effects of nivolumab (occurring in ≥ 0.01% to < 0.1% or ≥ 1/10,000 to < 1/1,000 patients):

- Severe allergic reaction (Anaphylactic reaction)
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids and diabetic coma
- Skin inflammatory reaction (Erythema multiforme)
- An autoimmune disorder associated with progressive muscle weakness or paralysis (Guillain-Barre syndrome)
- Inflammation of blood vessels

- Inflammation of the brain, potentially life-threatening or fatal
- Lung infiltrates, associated with infection or inflammation
- Muscle inflammation
- Neurologic syndrome characterized by muscle weakness (Myasthenic syndrome) including, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles (myasthenia gravis).
- An inflammatory disorder causing muscle pain and stiffness (Polymyalgia rheumatica)
- Muscle fiber released into the blood stream which could damage your kidneys (Rhabdomyolysis)
- Acne-like skin condition resulting in redness of face (Rosacea)
- A disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes (Sarcoidosis)
- Inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin (Stevens Johnson syndrome)
- A potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn (Toxic epidermal necrolysis)
- Disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains (Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis)

Lung inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.
Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans. Complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) after nivolumab.

Please inform your study doctor or nurse <u>AT ONCE</u> if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example, any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Risks of CT Scan
The contrast substance injected during the CT scan may cause pain, burning feeling, sweating and rarely a serious allergic reaction that can be serious. If you know you're allergic to iodine you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated and if you're older. In addition, your thyroid function may be affected. Please inform your doctor if this is the case.

CT imaging uses ionizing radiation, which increases your risk to develop cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation. The estimated additional lifetime risk of developing a potentially fatal cancer from a standard CT scan is approximately 1 in 2,000.

Risks of MRI Scan
Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation.

The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF) This causes a thickening of the skin, organs and other tissues, and is a rare complication in patients with kidney disease that undergo an MRI with contrast material. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

Blood tests
Collection of blood samples may cause pain, bleeding, bruising or infection. It is also possible that you may feel lightheaded or faint. Please tell your study doctor or the study nurse if you do not feel well after having your blood drawn at any time during your study participation.

Questionnaires
Filling out the questionnaires could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire. You have the right to refuse to answer any questions.

Research samples/Loss of Confidentiality
Your samples will be coded, however, there is a risk of loss of confidentiality of your information. If your samples are provided to research collaborators the following information may be made available: your diagnosis and treatments, the time the samples were collected in relation to your study regimen, your disease status, and

demographic data (for example gender, race, age, etc.). Please ask the Study Doctor or Study Coordinator if you would like to know more about how your information will be protected.

Pregnancy

Women

If you are a woman of child bearing potential, you must not have sexual intercourse or you must use reliable birth control throughout the study and for 6 months after the last dose of study drugs.

If you are pregnant or become pregnant or are nursing a child during the study, there may be risks to your unborn baby or nursing child. Some drugs cause premature (early) birth or birth defects. Nobody knows what all of these risks are right now.

If you become pregnant or think you may be pregnant during the study, immediately stop using the study drugs and contact the study doctor's office **immediately**. You must not breast-feed an infant during the study. Please also inform the study doctor if you become pregnant up to 6 months after the completion of the study drugs. If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use TWO types of birth control (one from each list below) AT THE SAME TIME.

You must use two types of birth control at the same time for medical reasons all during investigational study treatment (including during temporary breaks from investigational study treatment), and for at least 6 months after investigational study treatment has stopped. You must talk to the doctor before changing any birth control methods you have already agreed to use.

Primary forms
- tubal sterilization (tubes tied)
- partner's vasectomy
- intrauterine device

Secondary forms
- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide
- vaginal sponge (contains spermicide)

Any birth control method can fail. The reports of birth control failing are more frequent for female patients who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

Men

All men must use an acceptable form of birth control while taking part in the study and for 6 months after investigational study treatment has stopped because the effects on sperm are not known. Acceptable forms of birth control are male latex condom (with or without spermicide) or vasectomy. Also, men should not donate sperm or semen while taking part in the study because the effects on sperm are not known.

The study doctor must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you become pregnant during the study, the study doctor or his/her staff will ask to contact you and your pregnancy physician for information about the pregnancy until the child is born and may share this information with the sponsor.

If you are male, you should advise your study doctor if you father a child while participating in this study. The doctor will advise you on medical attention for your partner should this be necessary. We will ask for your partner's permission to collect information about the pregnancy and health of the baby.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may or may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
People who are not in a study are usually treated with either surgery, radiation, or with drugs. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more. The usual approaches to the treatment of kidney cancer are one of the following: high dose IL2 therapy, pazopanib, sunitinib, nivolumab, cabozantinib, axitinib, everolimus, lenvantinib with everolimus. This medication can enhance the immune response to your cancer and increase the amount of time without active disease. Some of the usual approaches to treatment of kidney cancer (specifically nivolumab and cabozantinib) have been shown to increase survival.

Instead of being in this study, you have these options:

- You may receive other available treatments for your cancer, such as those mentioned above
- You may be eligible for other cancer research studies.
- You may receive treatment for pain or other symptoms only.
- You may receive no treatment at all.

You should talk to your study doctor and your regular physician about each of your options and their risks and benefits before you decide if you want to take part in this study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
If you decide to leave the study early, please notify someone on the study team. They will instruct you on how to stop the study safely and you will be advised whether any additional test may need to be done for your safety.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

ESK981 will be provided by Esanik Therapeutics, Inc. free of charge.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Nivolumab
- Items or services needed to give you study drugs or devices (such as the cost of the infusion)
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services
- Treatment of complications

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Alva, at (734) 936-0091 or (734) 936-4000 (Hospital Operator – 24-hour paging). The doctor will either treat you or send you to another doctor for treatment.
You will get free medical care for any complication, injury, or illness caused by the study drug, device, or procedure. Esanik and the study doctor are responsible for determining whether your condition was the result of your participation in the study.

Esanik will pay for your treatment only if the need for treatment has been caused by the study drug, device or procedure. This means that you or your health plan must pay for any treatment that is part of your usual medical care or that is related to a medical condition you had before participating in the study.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will not be paid to take part in this study.

8.3 Who could profit or financially benefit from the study results?
Information obtained from this study may help the supporter Esanik Therapeutics, Inc. and/or the University of Michigan learn more about the causes, risks, treatments, or how to prevent this and other health problems. Esanik Therapeutics, Inc., the University of Michigan, and/or physicians at the university could profit financially from this information.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
The University of Michigan has rules to protect information about you. Federal and state laws also protect your privacy. Upon enrolling in this study, you will be assigned a unique identification number. All records related to the study will use this identification number instead of your name or other personally identifying information whenever possible. We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

You have the right to request access to your protected health information that is used or shared during this research and that is related to your study treatment for your disease, but you may access this information only after the study is completed. To request this information, please contact the researchers listed in Section 10 “Contact Information” (below).

Genetic Risks:
The federal 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 does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain 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 obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

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.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease or other communicable disease status
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University of Michigan, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Esanik Therapeutics, Inc. or safety monitors or committees, may need the information to:

  - Make sure the study is done safely and properly
  - Learn more about side effects
  - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular University of Michigan medical record.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?
As a rule, the researchers will not continue to use or disclose information about you but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:
- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help the University of Michigan and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:
- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished

- Express a concern about the study

Principal Investigator:	Ajjai Alva, MD
Mailing Address:	University of Michigan 1500 E. Medical Center Dr., 7316 CC Ann Arbor, MI 48109
Telephone:	(734) 936-0091
Emergency Contact:	(734) 936-4000 (Hospital Operator - 24-hour paging)

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?
You will receive a copy of the signed and dated informed consent

Your signature in the next section means that you have received copies of all of the following documents:
This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive,*

- *copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent to Collect and Store OPTIONAL Research Samples for Unspecified Future Research
This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to take part in this optional research. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep and store my blood and tissue samples for future research.

_____ No, I do not agree to let the study team keep and store my blood and tissue samples for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

UMCC 2018.052

PERSONAL CENSUS FORM

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]

2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

---

[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as “Haitian” or “Negro” are sometimes used in addition to “Black” or “African American.”)

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” is sometimes used in addition to “Hispanic” or “Latino.”