ID: UMCC 2018.044

NCT03639935

Rucaparib in Combination With Nivolumab in Patients With Advanced or Metastatic Biliary Tract Cancer Following Platinum Therapy

UNIVERSITY OF MICHIGAN CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: Phase II Multi-Center Study of PARP inhibitor Rucaparib in Combination with Anti-PD-1 Antibody Nivolumab in Patients with Advanced or Metastatic Biliary Tract Cancer Following Platinum Therapy

Company or agency sponsoring the study: The University of Michigan along with support from Bristol Myers Squibb (BMS) and Clovis Oncology

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

Principal Investigator:
Vaibhav Sahai, MBBS, MS 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:

Platinum-based combination chemotherapy, including gemcitabine and cisplatin is considered the standard of care treatment for newly diagnosed advanced unresectable or metastatic biliary tract cancer. However, mostly all patients eventually develop resistance to platinum-based chemotherapy and therefore tumor progression. It is also challenging to continue chemotherapy beyond 4 or 6 months due to side effects. Therefore, there is an urgent need to develop effective therapies that can be used to treat this cancer beyond platinum-based chemotherapy.

The purpose of this study is to test the effectiveness (how well the drug works), safety, and tolerability of the investigational drug combination of nivolumab plus rucaparib after 4 to 6 months of platinum-based chemotherapy treatment for advanced unresectable or metastatic biliary tract cancer.

Nivolumab (Opdivo) is a type of immunotherapy. Immunotherapy works by encouraging the body's own immune system to attack the cancer cells. Nivolumab has been approved by FDA for the treatment of multiple cancer, including but not limited to metastatic melanoma (a type of skin cancer), previously treated advanced lung, head & neck, liver and kidney cancers.

Rucaparib (Rubraca) is a poly (ADP-ribose) polymerase (PARP) inhibitor that has been approved by FDA for the treatment of ovarian, fallopian or primary peritoneal cancer previously treated with two or more chemotherapy regimens. Neither rucaparib nor nivolumab are currently approved by the FDA for treatment of patients with biliary tract cancer.

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 adenocarcinoma of the biliary tract that cannot be treated with surgery, transplant or ablative therapies (therapies that destroy abnormal tissue without removing the tissue).

There are many other inclusion and exclusion criteria 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 35 subjects at several institutions will take part in this study, including approximately 24 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 the 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, 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, CT or magnetic resonance imaging (MRI) of the upper and lower belly. The scans will be sent to a central location in a coded format.
    - 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.

- **Blood for biomarkers:** About 4 teaspoons of blood will be collected at each visit listed below. Samples will be collected at the following time points. *This is for research purposes.*
    - Pre-treatment: Cycle 1 Day 1
    - On-Treatment: Cycle 3 Day 1
    - Post-Treatment: End of Treatment (EOT)

<u>For patients at all sites excluding University of Michigan (use the below wording for tissue collection)</u>

- Tumor tissue samples. *This is for research purposes.*
    a. Pre-treatment Screening: A tissue block or slides from a previous biopsy will be collected for understanding the genetic and immune make-up of your cancer and its surrounding tissue. *This tissue has to be available for you to be able to participate in this study.*
    b. Post-treatment (optional): The tumor tissue samples will be obtained by core needle biopsy and up to 6 cores will be obtained, if possible. All biopsy related costs will be billed to your insurance; however, a CLIA certified 1600 targeted gene panel will be run on the tissue without additional cost to you and the report will be released with results to your treating doctor.
    c. <u>You can make your choice in Section 12 for optional biopsies.</u>

For patients at the University of Michigan only (use the below wording for tissue collection)

- Tumor tissue samples collected for research purposes:
    a. Pre-treatment: Screening: A tissue block or slides from a previous biopsy will be collected for understanding the genetic and immune make-up of your cancer and its surrounding tissue. *This tissue has to be available for you to be able to participate in this study.*
    b. On-treatment: Tumor tissue samples will be obtained by core needle biopsy after at least 6 weeks of therapy and up to 6 cores will be obtained, if possible. The cost of the biopsy will be covered by this clinical study.
    c. Post-treatment (optional): The tumor tissue samples will be obtained by core needle biopsy and up to 6 cores will be obtained, if possible. All biopsy related costs will be billed to your insurance; however, a CLIA certified 1600 targeted gene panel will be run on the tissue without additional cost to you and the report will be released with results to your treating doctor.
    d. <u>You can make your choice in Section 12 for optional biopsies.</u>

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.

On Day 1 and 15 of each cycle, you will receive nivolumab intravenously (through a vein in your arm or port) over a period of about 30-60 minutes. A cycle is defined as 28 days. You will also take rucaparib every day by mouth on days 1-28 of a cycle.

The researchers will ask you to complete a drug diary to track when you have taken your rucaparib. Please bring your drug diary and medication bottles (with extra tablets or empty) with you when you return for each appointment.

<u>Below are general rules for taking rucaparib:</u>

- Take rucaparib by mouth twice a day as close as possible to 12 hours apart; preferably at the same time every day
- Take with food or without food
- Swallow whole (do NOT chew, crush or cut the tablet)
- 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 4 hours of the scheduled time) DO NOT "make it up". Skip the missed dose and start taking rucaparib with the next scheduled dose.
- If you vomit any time after taking a dose DO NOT "make it up".

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

You may continue to receive nivolumab and rucaparib for up to 2 years as long as you are tolerating the treatment and your disease has not progressed.

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 study intervention visit 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:

Procedures	Screening	Cycle 1			Cycle X		End of treatment Visit	Follow-Up
		Day 1	Day 8	Day 15	Day 1	Day 15		
Medical History	X	X		X	X		X	X
Medication Review	X	X			X			
Physical Exam/Vital Signs	X	X		X	X	X	X	
Performance Status	X	X			X		X	
Routine Blood tests	X	X	X	X	X	X	CA 19-9 (or CEA)	
Pregnancy Test	X	X			X			
Scans/Imaging of your Cancer	X				Every 8 Weeks			
Research Blood		X			Cycle 3, Day 1		X	
Tumor Tissue / Biopsy	X				Cycle 3, Day 1		X	
Study Drug Administration		X		X	X	X		
Toxicity Evaluations		X		X	X		X	X
Survival Follow-up								X

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 blood, tumor tissue and medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

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. Their research may be similar to this study or may be completely different. 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. If you elect to proceed with the optional post-treatment biopsy, the results of the tests run on the tumor tissue samples will be released to your treating doctor. 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 sub-study (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. You will be contacted every 3 months for up to 2 years after you have stopped taking the study intervention.

4.3 When will my participation in the study be over?
The maximum time you will be in the study can be up to 3 years, but 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 the study team will follow you via telephone or an office visit every 3 months for up to 2 years from when you stopped taking the study intervention, or 3 years after the first date you started the study intervention. 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 biospecimens and collected information may be shared with BMS and Clovis. With appropriate permissions, your biospecimens 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.

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 RUCAPARIB

Oral rucaparib is an FDA approved drug for patients with ovarian, fallopian and primary peritoneal cancer but considered an experimental drug for biliary cancer and therefore may have side effects that cannot be predicted at this time. Rare or unknown side effects could possibly occur, including life-threatening events or death. If you experience certain side effects, your study doctor may decide to stop or lower your dose of study drug until you recover from the side effects.

The following is a list of the most commonly-reported side effects and other notable side effects considered to be possibly due to rucaparib, as reported by physicians about their patients who are taking rucaparib alone:

<u>Very Common (Occurring in 10% or more of patients)</u>

- Nausea
- Feeling tired (known as fatigue or lethargy)
- Changes in kidney and liver function blood tests. These changes will be evaluated by your study doctor along with any other side effects that you may be experiencing as well as other test results.
- Changes in your sense of taste
- Low blood counts, (red blood cells, white blood cells, and platelets). Sometimes fever occurs with the low blood counts. These effects may be more likely to occur after multiple cycles of treatment.
    - A low red blood cell count may make you feel tired or dizzy. If you feel dizzy while taking rucaparib, you should avoid potentially hazardous tasks such as driving or operating machinery.
    - A low white blood cell count puts you at higher risk for bacterial or viral infections. Having a high temperature or fever while your white blood cell count is low is a medical emergency and you must proceed to the nearest emergency room as soon as possible.

  - A low platelet count affects the ability of your blood to clot and could lead to bleeding events. Symptoms include but are not limited to, easy bruising, prolonged bleeding from cuts, blood in stools or urine, or nose bleeding
- Stomach-related effects such as constipation, vomiting, diarrhea, decreased appetite, stomach pain (epigastric pain), and indigestion.
- Increase in cholesterol. If your cholesterol increases significantly, your doctor may prescribe a medicine to lower your cholesterol level.
- A low phosphate level in your blood. Usually there are no symptoms but if the levels are critically low, you may notice trouble breathing, confusion, muscle weakness and/or irritability.
- Dizziness
- Difficulty breathing (dyspnea)
- Photosensitivity reaction
  - This is an immune system reaction to sunlight which causes itchy eruptions or areas of inflammation on patches of sun-exposed skin. It is advised that you avoid excessive sun exposure, wear protective clothing, and use sunscreens regularly (sun protection factor 50 or greater).
- Fever sometimes can occur independent of a low blood count. If you experience an elevation of your temperature, please refer to your study doctor for fever management.
- Difficulty sleeping

<u>Common (Occurring in 1% to less than 10% of patients)</u>

- Rash (also known as dermatitis) which will appear as changes in your skin color (e.g. redness) and texture (e.g. bumps, blisters, peeling). Some rashes may be itchy, painful, or cause no symptoms at all. This can vary in severity from mild to severe. In any case, please inform your study doctor immediately.
- Itchy skin (also known as pruritus)
- Upper Airway Infection (like the common cold)
  - You may experience infections involving the nose, pharynx, larynx, and sinuses. Symptoms include a blocked (congested) nose, a runny nose, and sneezing. You may also have clear discharge (mucus) from the nose. You may feel generally unwell and may also be associated with fever. Treatment is usually supportive, but if symptoms persist please inform your doctor.
- Inflammation of the mouth and lips (also known as stomatitis)
- Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in a very small number of patients treated with rucaparib during the safety period (while on treatment with rucaparib and 28 days after last dose). MDS is a pre-cancerous condition where the bone marrow is not as good at producing blood cells (red and/or white blood cells and/or platelets). People with MDS may need transfusions (red blood cells and/or platelets) and/or other treatments. In some cases, MDS can progress to AML, which is a cancer of the bone marrow where more abnormal and immature white blood cells (also called blasts) are made than normal white blood cells. People with AML need treatment with chemotherapy and/or a bone marrow transplant. Patients may develop AML without first being diagnosed with MDS.
- Events of MDS and AML have also been reported with PARP inhibitors similar to rucaparib. At this time, it is not known whether rucaparib or other PARP inhibitors cause MDS or AML, or if these

developed as a result of previous chemotherapy these patients received. Your Study Doctor will closely monitor your blood cell levels during treatment. If he/she has any concerns about your blood counts you may be asked to have a biopsy of your bone marrow.

Uncommon (Occurring in 0.1% up to less than 1% of patients)

- Lung inflammation (pneumonitis): Adverse events (AEs) of pneumonitis have been reported in a very small number of patients treated with rucaparib during the safety period (while on treatment with rucaparib and 28 days after last dose). 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 team 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.

Allergic Reactions

As with any drug, it is possible that you could have allergic reactions to study drug, such as itching, skin rash, facial swelling, and/or a severe or sudden drop in blood pressure. A sudden drop in blood pressure could lead to shock with loss of consciousness and/or possible seizures, including the possibility of death. If you have any of the above symptoms, seek medical attention right away.

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% of patients) are:

- Fatigue
- Skin rash
- Skin itching
- Diarrhea

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

- Abdominal pain
- 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
- Bilirubin increased: lab test result associated with abnormal liver function
- Chills
- Constipation
- Cough

- Creatinine increased: lab test result associated with decreased kidney function
- Decreased appetite
- Dry mouth
- Dry skin
- Fever
- Headache
- Lipase increased: lab test result associated with pancreas inflammation
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Joint pain or stiffness
- Loss of color (pigment) from areas of skin
- Low levels of sodium in blood
- Low platelet counts (thrombocytopenia): this may increase your risk for skin bruising, nose bleeds, and bleeding from the gums
- Low red blood cell counts (anemia): this may make you feel weak and tired
- Shortness of breath: Lung inflammation (pneumonitis - see details below)
- Nausea
- Pain in the muscles, bones, ligaments, tendons, and nerves
- Swelling, including face, arms, and legs (edema)
- Thyroid gland function increased or decreased
- 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 $\geq$ 0.1% to < 1% of patients):

- Allergic reaction
- Bronchitis: inflammation of the lining of the bronchial tubes, which carry air to and from the lungs
- Decreased secretion of hormones produced by adrenal glands
- Decreased thyroid stimulating hormone: a lab test associated with abnormal thyroid function
- Decreased secretion of hormones produced by pituitary gland
- Diabetes: a disease that results in too much sugar in the blood
- Dizziness
- Dry eye and blurry vision: inflammation of the eye
- Erythema multiforme: a skin disorder that is considered to be an allergic reaction to medicine or an infection. Symptoms may include symmetrical, red raised skins areas that can appear all over the body, more noticeable on the fingers and toes. These patches often look like “targets” (dark circles with purple-grey centers)
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- Blood pressure: high or low
- Hives
- Inflammation of the stomach
- Kidney function failure or kidney disease: inflammation of the kidney
- Low white blood cell counts (neutropenia): these put you at higher risk for infection

- Psoriasis: characterized by patches of abnormal, scaly skin
- Respiratory failure: a condition in which not enough oxygen passes from your lungs into your blood, or when your lungs cannot properly remote carbon dioxide.
- Trouble falling and/or staying asleep (insomnia)
- Upper respiratory tract infection

Rare side effects of nivolumab (occurring in≥ 0.01% to < 0.1% patients):

- A malfunction of the immune system that produces autoantibodies, which attack red blood cells as if they were foreign substances to the body (autoimmune hemolytic anemia)
- Severe allergic reaction may include but not limited to high grade fever, rash, swelling and pain (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
- Double vision
- 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
- 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).
- Swelling and irritation of the thin saclike membrane surrounding the heart (pericarditis)
- 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)
- Heart Failure - the severity level can be complicated and lead to death: inflammation of the heart

The following events have been identified during post-approval use of nivolumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

- Graft-versus-host-disease: a condition that occurs when donor bone marrow or stem cells attack the recipient
- Hemophagocytic lymphohistiocytosis (HLH) syndrome: a disease that may affect your body's defense system, called immune system. Certain white blood cells may attack other blood cells. These abnormal blood cells collect in your spleen and liver, causing these organs to enlarge. The symptoms may include fever, rash, and low blood cell counts

- Solid organ transplant rejection
- Vogt Koyanagi Harada syndrome: a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision; the ear leading to hearing loss, ringing in the ears and /or the skin leading to loss of skin color

Lung inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported 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 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
Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include dizziness and fainting.

Tumor Biopsy
A piece of a tumor will be removed for testing. Potential risks and discomforts that you may experience as a result of the procedure depend upon the location of the tumor. The more common risks/discomforts include pain, bleeding, infection, damage to tissues, and healing complications. Your doctor will further explain any specific risks that may apply based on the procedure, and you will sign a separate consent for the procedure which will provide risk information in more detail. In order to make the procedure more comfortable, you will get a local anesthetic to numb the area. A mild sedative may also be given to you.

- Genetic material, including DNA and RNA, will be obtained from samples, stored in freezers, and used for profiling and analyzing your cancer. Specifically, the study includes DNA sequencing of your tumor and normal cells as a comparison. The goal is to identify key changes in the genes important to cancer cells that could potentially influence clinical decision making for your cancer. However, success or clinical benefits from the profiling of your cancer DNA is not guaranteed.

- Some cells from your tumor may be grown and used to create cell lines that can be used as an ongoing source of genetic material or used for laboratory research. Additional analysis of the sequencing data will be used for research purposes, for example to discover new, unknown associations between genes and cancer. This type of research may affect the lives of future patients with cancer.

- It is possible that a mutation found in the tumor DNA is also a mutation in your normal tissue (inheritable, or passed down in families). Your study doctor will discuss this result with you. If your test results show that you have gene mutations that are inherited, your doctor should recommend that you meet with a genetic counselor. This referral is considered standard care and is not part of this study.

- As with all medical screening tests, there is a chance of a false positive or a false negative result. A "false positive" refers to the identification of a genetic change that is not present. A "false negative" is the failure to find a genetic change that indeed exists. The tests have been designed to ensure that the possibility of incorrect results is low.

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.). See section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

Pregnancy
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 treatment (including during temporary breaks from treatment), and for at least 6 months after 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 7 months after 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 and for 7 months following the last dose of study drug 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 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 not receive any direct 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?
You do not have to be in this study to get treatment for your cancer. Other possible options include:

- Continue with your platinum-based chemotherapy
- Change treatment to other standard of care regimens such as irinotecan with 5FU or FOLFIRI, oxaliplatin with 5FU or FOLFOX, if appropriate.
- You could participate in other research trials
- You could be a candidate for liver directed therapy or palliative radiation
- You may also choose not to receive any further treatment.

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.

Rucaparib will be provided by Clovis Oncology free of charge.

Nivolumab will be provided by BMS 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
- 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 Vaibhav Sahai immediately, at 734-936-4991 (office) 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 at the UMHS for any hospitalization or ER visits related to an acute condition or

injury that was directly caused by the study drug, device, or procedure. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study.

The UMHS 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.

It is not the policy of the federal funding agencies to compensate or provide medical treatment for human subjects in federally funded studies.

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 supporters BMS and Clovis Oncology and/or the University of Michigan learn more about the causes, risks, treatments, or how to prevent this and other health problems. BMS, Clovis Oncology, 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

Some data collected from you may be deposited into the database of Genotypes and Phenotypes (dbGAP) but all identifiable information will be removed prior to submission so that the data cannot be linked to you in any way. The database of dbGaP is a database developed by the National Center for Biotechnology Information (a division of the National Library of Medicine) to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype. All data submitted from this study will only be available through controlled access and restricted to cancer research studies. Any researcher requesting access to the data must formally apply to dbGAP and present a research study rationale for why they need access to the data. The data may also be submitted to other future database systems which will have similar access controls as dbGAP utilizes.

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.
- BMS, Clovis Oncology, 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 University of Michigan and government officials make sure that the study was conducted properly

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: Vaibhav Sahai, MBBS, MS
Mailing Address: Department of Internal Medicine, Division of Hematology/Oncology
1500 E. Medical Center Drive
C412 MIB, SPC 5848
Ann Arbor, MI 48109-5848

Telephone: 734-936-4991 (Office)
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

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received signed and dated copies of all of the following documents:

- This "Consent to be Part of a Research Study" document.
- 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.

Print Legal Name: _____

Signature: _____

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

Consent/Assent for Participating in Optional Research Biopsy

This project involves optional biopsies for research purposes. I understand that it is my choice whether or not to take part in this optional research biopsy. 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.

Post-treatment research biopsy

_____ Yes, I agree to take part in the optional post-treatment research biopsy.

_____ No, I do not agree to take part in the optional post-treatment research biopsy.

Print 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.

Print Legal Name: _____

Title: _____

Signature: _____

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

U of M Study #2018.044

PERSONAL CENSUS FORM

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Rogel 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."