ID: UMCC 2019.116	Gemcitabine and Cisplatin With or Without CPI-613 as First Line Therapy for Patients With Advanced Unresectable Biliary Tract Cancer (BilT-04)	NCT04203160

UNIVERSITY OF MICHIGAN CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: A Multi-Center Randomized Phase IB/II Study of Gemcitabine and Cisplatin With or Without CPI-613 as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer (BilT-04)

Company or agency sponsoring the study: The University of Michigan along with support from Cornerstone Pharmaceuticals

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.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying a new study drug intervention in a small group of people to learn about its safety and how well it works as a treatment option for patients with advanced biliary tract cancer. Researchers want to understand how the drug works in your body and how your body will react to it. This research will find out about the safety and efficacy of CPI-613 (devimistat) in the treatment of advanced biliary tract cancer when used in combination with standard of care chemotherapy (gemcitabine plus cisplatin) compared to gemcitabine and cisplatin alone. Your health-related information and blood and tissue samples will be collected for this research study.

The phase 2 portion of this study involves a process called randomization. This means that the study drug intervention you receive in the study is not chosen by you or the researcher. The study design divides study participants into separate groups, based on chance (like the flip of a coin), to compare different study drug interventions or procedures. If you decide to be in the study, you need to be comfortable not knowing which study group you will be assigned.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks of CPI-613 may include vomiting, low blood counts, liver problems, and inflammation around the injection area where the study drug is given. You could experience an allergic reaction to CPI-613 or to any combination of the drugs used in this study. For standard of care chemotherapy, a brief list of some of most commonly seen risks may include nausea, vomiting, infection, loss of appetite, bruising, fatigue, rash, pain, hair thinning and abnormal lab tests. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but may benefit others in the future by helping people to live longer or improve the quality of life.

We expect the amount of time you will participate in the study to vary depending on how your disease responds to the study intervention and if you have any major side effects and could be up to 3 years including follow-up.

You can decide not to be in this study. Alternatives to joining this study include receiving standard of care treatment for this disease, taking part in a different study, receiving palliative care, or having no treatment.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This is a Phase I/II study which means that the goals are to see if the combination of CPI-613, gemcitabine and cisplatin is safe as well as whether it is effective in improving outcomes. The first part of the study will try to find out what effects, good and/or bad, this drug combination has on you and your cancer, and to find a dose to use in the second part of the trial. CPI-613 is an experimental drug which is not approved by any Health Authorities anywhere in the world for the treatment of advanced biliary tract cancer. Platinum-based combination chemotherapy, including gemcitabine and cisplatin is considered the standard of care treatment since it has demonstrated a survival benefit for patients with advanced biliary tract cancer.

CPI-613 is thought to kill cancer cells by turning off their mitochondria. Mitochondria are used by cancer cells to produce energy and are the building blocks needed to make more cancer cells. By shutting off these mitochondria, CPI-613 deprives the cancer cells of energy and other supplies that they need to survive and grow in your body. Research shows that CPI-613 when used alone is not effective for the treatment of advanced biliary and pancreatic cancer. We want to find out what effects, good and/or bad, CPI-613 has on you and your cancer when given along with standard chemotherapy with gemcitabine and cisplatin. In addition, we want to study your tissue (biopsy) sample(s) to see if certain genes can identify subjects that would benefit the most from this combination of CPI-613 plus gemcitabine and cisplatin.

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?

Adults who have cancer of the biliary tract that cannot be treated with surgery, transplant or ablative therapies (therapies that destroy abnormal tissue without removing the tissue). This study involves two groups of subjects. One group will receive gemcitabine and cisplatin with CPI-613. The other group will receive gemcitabine and cisplatin alone.

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 68-78 subjects at several institutions will take part in this study, including approximately 35 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 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.

Subjects who qualify for this study will be informed of the current Phase since it will impact their treatment options. During Phase I, all subjects will be assigned to gemcitabine and cisplatin with CPI-613. During Phase II, subjects will be assigned the treatment arm randomly by chance (e.g., flip of a coin) to get one of the following study drug interventions:

- Study Drug Intervention Arm A: Gemcitabine and cisplatin with CPI-613
- Study Drug Intervention Arm B: Gemcitabine and cisplatin

During Phase II, you will have a sixty-seven percent (67%) chance of getting assigned to study drug intervention Arm A, and a thirty-three percent (33%) chance of getting assigned to study drug intervention Arm B. This is an open label study, which means that both you and your study doctor will know what study drug intervention you are assigned to.

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 review**: 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, 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 on some visits listed in the table below. *This is for research purposes.*

- **Tumor tissue samples:** *This is for research purposes.*
    a. Pre-treatment Screening: A tissue block or slides from a previous biopsy or surgery will be collected for understanding the genetic and immune make-up of your cancer and its surrounding tissue, if available. *If this tissue is not available, you will still be able to participate in this study.*
    b. Post-treatment (optional): A tissue block or slides from a standard of care biopsy will be collected, *if available*, for understanding the effect of the CPI-613 and chemotherapy on genetic and immune make-up of your cancer and its surrounding tissue.

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.

For this study a cycle is defined as 3 weeks.

For subjects in Phase I and Phase II Arm A:
On Day 1 and Day 8 of each cycle, you will receive the following study intervention:

- CPI-613 intravenously (through a vein in your arm or port) over a period of about 120 minutes.
- Gemcitabine intravenously (through a vein in your arm or port) over a period of about 30 minutes.
- Cisplatin intravenously (through a vein in your arm or port) over a period of about 30-60 minutes.

For subjects in Phase II Arm B:
On Day 1 and Day 8 of each cycle, you will receive the following study intervention:

- Gemcitabine intravenously (through a vein in your arm or port) over a period of about 30 minutes.
- Cisplatin intravenously (through a vein in your arm or port) over a period of about 30-60 minutes.

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 the study intervention for up to 2 years as long as you are tolerating the study intervention 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	Phase IB or II Arm A			Phase II Arm B			EOT Visit	Follow-Up Q3 months +/- 1 week
		Cycle 1	Cycle X		Cycle 1	Cycle X			
		Day 1	Day 1	Day 8	Day 1	Day 1	Day 8		
Informed Consent	X								
History, Physical Examination	X	X	X		X	X		X	
Weight, BSA	X	X	X		X	X		X	
Vital Signs	X	X	X	X	X	X	X	X	
Performance Status	X	X	X		X	X		X	
Toxicity Evaluations		X	X	C1D8	X	X		X	
Scans with Tumor Measurements	X		X+			X+			
CBC with differential	X	X	X	X	X	X	X		
CMP	X	X	X	X	X	X	X		
HbA1c	X		X@			X@			
CA 19-9, CEA		X	X		X	X		X	
PT, PTT	X								
Pregnancy Test	X								
Concomitant Medication Review	X	X	X		X	X			
ECG	X								
Research Blood		X	X#		X	X#		X	
Tissue	X							X	
Study Drug Administration		X	X	X	X	X	X		
Survival Follow-up									X

Once after Cycle 3
+ Every 8 weeks
@ Every 6 weeks

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 (such as gender, race, and how your cancer responded to the treatment etc) 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. 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 (such as gender, race, and how your cancer responded to the treatment, etc). 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 office visit is expected to take approximately 4-6 hours. You will have an office visit or be contacted by a member of the study team 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 we will follow you via telephone or 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, whichever is earlier. 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 Cornerstone Pharmaceuticals. 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 delay or even discontinue the study intervention, including the standard chemotherapy (gemcitabine and cisplatin) if the side effects are too serious.

The known or expected risks are:

Side Effects ASSOCIATED WITH GEMCITABINE

COMMON, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:
• Mild nausea or vomiting • Low white blood cells and risk of infection • Low levels of platelets (blood cells that help to form clots) • Fatigue or tiredness • Decrease in red blood cells (anemia) causing weakness or fatigue • Fever and flu-like symptoms (body or muscle/joint aches/pains) • Mild skin rash • Shortness of breath • Elevation in liver blood tests • Loss of circulating protein in urine

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, from 4 to 20 may have:
• Pain and irritation along the vein where the drug is given • Bleeding • Red blood cell or platelet transfusion due to low blood counts • Infection • Allergic or hypersensitivity reactions • Diarrhea • Constipation • Thinning of hair (alopecia) • Swelling and fluid retention in the belly, legs or lungs • Mouth sores or ulcers

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, from 4 to 20 may have:
• Increased sleepiness

RARE, AND SERIOUS In 100 people receiving Gemcitabine, 3 or fewer may have:
• Reaction to chemotherapy during infusion • Lung inflammation causing serious breathing difficulty • Kidney failure • Liver failure • Abnormal heart rhythm and heart failure • Confusion • Severe infection (sepsis) • Stroke

Side Effects ASSOCIATED WITH CISPLATIN

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Nausea or vomiting • Decrease in appetite • Low white blood cells and risk of infection • Low levels of platelets (blood cells that help to form clots) • Fatigue or tiredness • Decrease in red blood cells (anemia) causing weakness or fatigue • Hair loss (alopecia) • Changes in kidney function, which if serious can cause kidney failure (rare) • Elevated blood glucose levels

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Fever • Allergic or hypersensitivity reactions • Diarrhea • Change in taste • Mouth sores or ulcers • Ringing in the ears • Hearing loss • Pins and needles in the fingers and toes (neuropathy) • Transient elevation of liver blood test • Disturbances of salts in the blood (e.g., sodium, calcium and magnesium) • Formation of presence of a blood clot inside a blood vessel (thromboembolic event) • Pain and irritation along the vein where the drug is given • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Infection • Bleeding • Low blood pressure • Blurred vision with color changes • Dizziness

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• Kidney failure • Rash • Muscle cramps • Blood cancer (e.g. leukemia) • Confusion • Seizures

Side Effects ASSOCIATED WITH CPI-613

The study drug is being investigated for use in humans. Please carefully read the sections on risk and benefits below. Not all of the side effects are known at this time. If you choose to take part in this study, it is very important that you let the study team know of any symptoms you have.

Some potential risks associated with CPI-613 have been determined from previous animal studies and studies in humans. In laboratory animals, side effects included swelling around the injection site causing redness and pain. To avoid this potential side effect, CPI-613 will be given to you through a central venous catheter. There may be other more severe side effects such as tiredness and increased production of saliva and tears. Significant side effects have also caused some deaths in test animals at dose levels that are higher than those to be used in this study. Many side effects may go away shortly after being given CPI-613 but in some cases, side effects may be severe, long lasting, or may not go away. Although not yet reported in any human subjects, it remains possible that CPI-613 might cause your disease to progress or produce a fatal side effect. CPI-613 may also cause side effects that we have not yet seen and cannot predict. The side effects determined from human studies are listed below.

COMMON, SOME MAY BE SERIOUS In 100 people receiving CPI-613, more than 10 and up to 40 may have:
• Allergic or hypersensitivity reaction • Diarrhea which may be from colitis or enterocolitis (inflammation of the colon and/or small intestine) • Nausea and vomiting • Dehydration which may be from vomiting or diarrhea • Change in taste sensation • Mouth sores or ulcers • Tiredness • Changes in liver function • Changes in kidney function, which if serious can cause kidney failure (rare)

COMMON, SOME MAY BE SERIOUS In 100 people receiving CPI-613, more than 10 and up to 40 may have:
• Too much or too little calcium in the blood • Decrease in red blood cells (anemia) causing weakness or fatigue • Low white blood cells and risk of infection, such as pneumonia (lung infection), sepsis (a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs) • Low levels of platelets (blood cells that help to form clots) • Disturbances of salts in the blood (e.g., calcium and potassium) • Elevated blood glucose levels

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving CPI-613, from 4 to 10 may have:
• Headache • Constipation • Lightheadedness • Low blood pressure • Abdominal pain

RARE, AND SERIOUS In 100 people receiving CPI-613, 3 or fewer may have:
• Cerebrovascular accident (stroke)

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 also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Electrocardiogram (ECG)

An ECG shows the electrical activity of the heart by placing several small adhesive pads that are attached to wires on your chest and limbs (called leads) and connecting them to a machine that reads the signal. There may be minor discomfort, similar to removing a bandage, when the electrodes taped to your chest are removed.

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 Tissue
A piece of a tumor will be collected for testing, if available from prior surgery or biopsy.

- Genetic material, including DNA and RNA, may be obtained from samples, stored in freezers, and used for profiling and analyzing your cancer. Specifically, the study may include 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 the efficacy of chemotherapy and CPI-613. This analysis is dependent on the availability of additional funding and will likely not be done until after the study has completed. The results will not be released to you.

- Some cells from your tumor may be grown, when possible, 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.

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 study intervention (including during temporary breaks from study intervention), and for at least 6 months after study intervention 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 study intervention 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 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:

- Standard of care treatment options include gemcitabine and cisplatin, or gemcitabine and oxaliplatin
- Additional treatment options including oxaliplatin with 5FU (or FOLFOX), if appropriate can also be utilized.
- If you have an unresectable or metastatic MSI-H (microsatellite instability-high) or dMMR (mismatch repair deficient) solid tumor that has progressed after prior treatment you could change treatment to pembrolizumab if you have no satisfactory alternative treatment.
- 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.

CPI-613 will be provided by Cornerstone l Pharmaceuticals free of charge until trial completion. After the completion of the trial, Cornerstone Pharmaceuticals will not continue to supply CPI-613 to study subjects.

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
- Gemcitabine and cisplatin
- 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

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.

Some health plans will not cover the cost of standard treatments when they are combined with investigational treatments. It is important that you work with the study team to confirm your health plan with cover the costs of the gemcitabine and cisplatin if you take part in this study.

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. Sahai immediately, at 734-936-4911 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. The supporting company (Cornerstone Pharmaceuticals, Inc.) and the study doctor are responsible for determining whether your condition was the result of your participation in the study. Cornerstone Pharmaceuticals 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?
The company whose product is being studied: Cornerstone Pharmaceuticals

The University of Michigan has filed a patent related to the treatment in this study. That means the University, Dr. Sahai, and Cornerstone Pharmaceuticals could one day benefit financially if the treatment is approved by the FDA. In the interest of transparency, you should know that Dr. Sahai is a paid consultant to Cornerstone Pharmaceuticals.

The University of Michigan is receiving payments from Cornerstone Pharmaceuticals to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from Cornerstone Pharmaceuticals for conducting this study.

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

We will collect and store information about your genes. The DNA contained in your genes holds the instructions that your body uses to grow and function. Your genes are responsible for your physical features such as eye color, blood type, and how your body breaks down medications. Genes can also be responsible for some medical conditions.

Genomic information relates to the structure and function of all of the genetic material in the body.

We will submit your genomic information to a repository to be used for scientific purposes. A repository contains information from many people. Some repositories are maintained by the University of Michigan, some are maintained by the federal government, and some are maintained by private companies.

Researchers all over the world can take information from the repository and use it in their studies. Their studies may be similar to this one or may be completely different.

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. Genomic summary results should be kept restrictive.

We will label your genomic information with a code, instead of your name or other information that people could use to directly identify you. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally.

If you allow us to put your genomic information in the repository, you can change your mind later and ask us to remove it. Keep in mind, however, that we cannot take back information that other researchers have already obtained from the repository.

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.
- Cornerstone Pharmaceuticals, 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

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: University of Michigan
1500 E. Medical Center Dr.
Ann Arbor, MI. 48109
Telephone: 734-936-4991
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?

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.

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

_____ (initials) 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): _____