MC200402 / 20-007235

Phase 2 Study of FGFR Inhibitor Futibatinib in Combination with Anti-PD1 Antibody Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma with FGF19 Expression

NCT04828486

Document Date: 03/13/2024

MAYO CLINIC

Name and Clinic Number
Protocol #: MC200402 **Version #: Main Study Consent** **Version Date: A5 08Dec2023**

Approval Date: **March 13, 2024**
Not to be used after: **March 12, 2025**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC200402 - Phase II Study of FGFR Inhibitor Futibatinib in Combination with Anti-PD1 Antibody Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma with FGF19 Expression (Main Study)

IRB#: 20-007235

Principal Investigator: Nguyen H. Tran, M.D., Aminah Jatoi, M.D., and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to evaluate the possible risks of futibatinib when taken with pembrolizumab. Futibatinib is an investigational Fibroblast Growth Factor Receptor (FGFR) inhibitor which may inhibit the growth of certain cancer cells in humans. FGFR gene amplification is a genetic marker that is present in some cancers. This drug may therefore help in the treatment of your advanced liver cancer since your cancer has a specific FGFR gene amplification.

	You have been asked to take part in this research because you have liver cancer called "hepatocellular carcinoma" or HCC, which has spread outside your liver, called "metastatic cancer."
What's Involved	Study participation involves about the same amount of time as regular care for your cancer. Before you can take part, you will need to have a biopsy of your cancer. If your tumor tissue has not been tested previously, we will also test a portion for FGF-19, a biomarker for some cancers. If you choose to take part in this study you will come to the clinic every 21 days. You will be given pembrolizumab, which is an immune therapy agent approved by the FDA for use in HCC. And you will receive an oral drug, called "futibatinib," which is investigational.
Key Information	There are alternatives to taking part in this research. The research team will discuss the other treatment options with you. The main risks from this study are due to the drugs being used to treat your cancer. Futibatinib is an investigational drug which has not been approved by the FDA, although the FDA is allowing futibatinib to be used in this study. Futibatinib can cause a build-up of calcium/phosphate salts or lesions in organs or body parts (e.g., heart, blood vessels, lung, stomach, intestine, tongue, kidney, urinary bladder, eye, bone, cartilage, brain, adrenal gland, and skeletal muscle). This build-up may lead to increased risks of several medical conditions such as bone disorders, joint cartilage disorders, eye disorders, heart failure, renal failure, liver failure, or even death. The risks associated with study participation are completely described later in this form. Be sure to review them thoroughly. There are no additional costs to you for taking part in this study. The costs are described later in this consent form. Be sure to review them completely. While our study is research and not guaranteed to offer help, you may benefit from the treatment if it works.

Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

Contact Information

If you have questions about …	You can contact …
• Study tests and procedures • Materials you receive • Research-related appointments • Research-related concern or complaint • Research-related injuries or emergencies • Withdrawing from the research study	**Principal Investigator:** Dr. Nguyen Tran (MN) **Phone:** MN: (507) 284-2511 **Institution Name and Address:** Mayo Clinic 200 1st Street SW Rochester, MN 55905
• Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
• Rights of a research participant • Any research-related concern or complaint • Use of your Protected Health Information • Stopping your authorization to use your Protected Health Information • Withdrawing from the research study	**Research Participant Advocate (RPA)** **(The RPA is independent of the Study Team) Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchparticipantadvocate@mayo.edu
• Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:
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.

A description of this research study will be available on http://www.clinicaltrials.mayo.edu. This Web site will not include information that can identify you. You can search this Web site at any time.

Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have hepatocellular carcinoma (HCC) that is advanced or has metastasized.

About 25 people will take part in this study at Mayo Clinic.

Why is this research study being done?

This is a clinical research trial of a study drug, futibatinib (LYTGOBI®), which is a drug under investigation. This means that futibatinib has not been approved for use in hepatocellular carcinoma. Futibatinib is an investigational Fibroblast Growth Factor Receptor (FGFR) inhibitor which may slow or stop the growth of certain cancer cells in humans. FGFR gene amplification is a genetic marker that is present in some cancers. Futibatinib is approved by the FDA for the treatment of patients with cholangiocarcinoma that harbors FGFR2 gene alterations. This drug may therefore help in the treatment of your advanced liver cancer if your cancer has a specific FGFR gene amplification.

The purpose of this study is to evaluate whether futibatinib plus pembrolizumab has an effect on advanced liver cancer and to find out what side effects may happen.

Futibatinib is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced liver cancer. However, the FDA has allowed the use of this drug in this research study.

Information you should know

Who is Funding the Study?
National Comprehensive Cancer Network (NCCN) is providing a grant to Mayo Clinic to cover the costs of running the study. This study was approved and funded in part by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Taiho Oncology, Inc. Taiho Oncology, Inc. will provide the study drug, futibatinib, for the study. Neither NCCN nor Taiho Oncology, Inc. are study sponsors.

Information Regarding Conflict of Interest:
Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

You will be in this study until your cancer gets worse ("progresses"), or you have side effects that you cannot tolerate.

What will happen to you while you are in this research study?

Before you can take part in this study you will need to have a biopsy of your liver cancer.

If your tissue has not already been tested, a portion from the biopsy will be checked to see if you have a biomarker called FGF19.

If you are eligible and willing to take part in this study, you will sign this informed consent form and have the following:

- Collect blood samples (about 2.5 tablespoons) for research before you start treatment.
- Nutrition consult to help you understand a low phosphate diet
- Medical history and physical exam including vital signs (temperature, blood pressure)
- Eye exam
- Routine blood testing
- Imaging of your cancer
- Pregnancy test if you are able to become pregnant

Once you start the study, you will be treated in cycles. A treatment cycle is defined as 21 days. The study drug, futibatinib is taken by mouth (oral) every day.

You should take your assigned futibatinib dose with a glass of water with or without food. Futibatinib should be taken every 24 hours in the morning or evening at the same time each day, if possible. You will be given a diary to record when you take your futibatinib. You should bring this diary and your pill bottles to every appointment.

In addition, you will be given pembrolizumab by intravenous (IV) infusion on Day 1 of Cycle 1; and on Day 1 of all subsequent cycles thereafter. You can receive pembrolizumab for up to 2 years.

During the first treatment cycle you will need to return to the clinic for testing every week (on Days 8 and 15), for your safety.

If you agree to participate in this trial, the following tests, examinations, or procedures will be done on the schedule described below in order to find out if you are eligible to enter the trial, to monitor your health, and to measure how your cancer responds to the trial drug after you have entered the trial.

As part of hyperphosphatemia management, you will need to limit your phosphate intake - avoidance of foods that are especially high in phosphate, e.g., dairy products, meats, nuts, and other high-protein foods, processed foods, and colas (e.g., Pepsi, Coke, etc.). Your study doctor will provide you more details about this diet.

Futibatinib and pembrolizumab can affect your vision, so you will need to have an eye exam prior to starting the trial and again about every 2 months after starting the trial for the first six months. After the first six months, the eye exams can be every 3 months. If you notice any changes in your vision notify your doctor right away.

Day	**What will happen**
Screening	• Your tissue will be tested for FGF-19 • Biopsy of your cancer
Prior to starting the trial	• Physical exam including complete medical history, height, weight and vital signs (blood pressure, pulse, temperature) • ECOG performance status (assessment of your ability to carry out daily activities) • Routine blood tests • Routine testing for AFP AFP-L3% if you have HCC • Routine imaging of your tumors to determine their size and location before starting the study (usual imaging methods include PET/CT, CT, and MRI) • Routine eye exam if you have not had one recently

Day	What will happen
	• Pregnancy test if you are able to become pregnant • Nutrition consult to learn how to manage phosphorus in your diet • Research blood collection (less than 3 tablespoons)
Prior to Day 1 of every cycle	• Physical exam including complete medical history, weight and vital signs (blood pressure, pulse, temperature) • ECOG performance status • Routine blood tests
Cycle 1, Day 1	• Receive pembrolizumab into a vein or port if you have one • Start taking futibatinib by mouth once per day with water
Days 1-21 of every cycle	• Take futibatinib daily at the same time
Cycle 1, Day 8 and Day 15	• Routine blood tests for safety
End of Cycles 3, 6, 9, etc	• Routine imaging of your tumors • Routine testing for AFP AFP-L3% if you have HCC • Routine eye exam • Research blood collection (less than 3 tablespoons)
End of treatment	• Physical exam including complete medical history, weight and vital signs (blood pressure, pulse, temperature) • ECOG performance status • Routine blood tests • Routine imaging of your tumors • Routine testing for AFP AFP-L3% if you have HCC • Research blood collection (less than 3 tablespoons)
Safety follow-up Visit - 30 days after your last dose of study drug	• Physical exam including complete medical history, weight and vital signs (blood pressure, pulse, temperature) • ECOG performance status • Routine blood tests

Tests done only for research purposes are not meant to provide clinical information or help care for you. The results are only important for research. Therefore, the results of tests done with your information and samples will not be provided to you. In the rare event that a finding might affect the health of you or your family, we will contact you and you can choose whether to receive or refuse the information. If you decide to follow up and further medical testing or care is needed, the costs will be billed to you or your insurance.

Treatment discontinuation

When you stop treatment on this study, you will have the following tests and procedures if they have not been done recently. Your doctor will determine which ones are needed. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- Routine imaging of your cancer

We will also draw some blood for research testing (40 ml or about 3 tablespoons) at the time of treatment discontinuation or if the cancer comes back.

Safety Follow-up

About 30 days after your last treatment with futibatinib, you will have the following tests and procedures if they have not been done recently. Your doctor will determine which ones are needed. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests

Follow-up visits

After you have finished all your treatment, you will have the following tests and procedures once every three months for the first year and then once every four months for two more years:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests

Optional Research Testing

Research Questionnaires

During this study, we will ask you to fill out questionnaires about your general health and well-being. These questionnaires are optional. If you agree to participate in these optional questionnaires, we hope that you will answer all of the questions, but you can skip any questions you don't want to answer. The questionnaires will take about 15 minutes to complete.

Research Tissue Collection

If your cancer returns, and a biopsy of the recurrent tumor is collected, we would like to obtain a portion of the biopsy tissue for research testing. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better

understand how to make this therapy more effective. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only, and you will not have to pay for them.

You can take part in the treatment portion of this study without taking part in these research tests.

Please mark your choices for each question below:

1. I am willing to complete questionnaires about my health and well-being while I am taking part in this study:

☐ Yes ☐ No Please initial here: _____Date: _____

2. If my cancer comes back and a biopsy or surgery is done, I agree to allow Mayo Clinic to obtain tissue sample(s) from my biopsy or surgery for research testing planned as part of this study.

☐ Yes ☐ No Please initial here: _____Date: _____

What are the possible risks or discomforts from being in this research study?

Side effects of futibatinib
Very common side effects (seen in at least one of every 10 people who took futibatinib) are:

- Increased level of phosphorus in the blood (Hyperphosphatemia) (usually no symptoms) which may result in muscle cramps, numbness, or tingling around the mouth
- Nail disorders which may include separate of the nail from the skin, shedding, change in color, infection, damage, or pain
- Diarrhea
- Hair loss
- Dry mouth
- Increased blood level of liver enzymes -abnormalities in blood tests (AST, ALT) that measure how well the liver is working, which may indicate liver damage
- Dry skin
- Tiredness and lack of energy
- Inflammation of the mouth
- Redness, swelling, and tenderness on the hands and feet, which may cause blistering and peeling of skin (hand-foot syndrome)

- Nausea
- Difficulty in passing stool (constipation)
- Reduced desire to eat (decreased appetite)
- Changes in taste, distortion or loss of sense of taste
- Dry eye
- Joint pain
- Muscle pain

Common side effects (seen in at least 1 of every 100 people who took futibatinib) are:

- Vomiting
- Weight loss (lowered weight)
- Weakness, having no energy
- Sudden, involuntary contraction of one or more muscles (muscle spasm)
- Tremor – involuntary, rhythmic muscle contraction leading to shaking movements in one or more parts of the body
- Muscle weakness
- Increased blood level of creatinine, which can be a sign of damage to the kidneys
- Increased blood level of an enzyme called alkaline phosphatase, which can be a sign of damage to liver or bone
- Increased calcium in the blood, which may cause muscle cramps, confusion, tingling in the lips, and/or stiff, achy muscles
- Low red blood cell counts (anemia), which may cause shortness of breath and tiredness
- Low platelet cell counts (thrombocytopenia) which help to clot blood
- Blurred vision, vision problems
- High level of enzyme from muscle in the blood (increased creatine phosphokinase) – can be a sign of possible muscle damage or muscle breakdown
- Heartburn
- Chronic heartburn and indigestion (also known as “GERD”)
- Yellowish color in the skin or eyes (jaundice), which is usually caused by liver disease and a high level of bilirubin in the blood
- Dizziness
- Itching
- Abdominal (belly) pain – feeling of fullness or tightness
- Low white blood cell counts (neutrophils and lymphocytes), which may increase the risk of a severe infection
- Nerve damage or disorders (e.g. weakness, loss of muscle coordination, numbness, pain
- Nose bleeding
- Dryness in the nose

- Pain in the hands or feet
- Urinary tract infection
- Rash
- Reduced sense of touch or sensation including temperature
- Headache – persistent headache or migraine
- Clouding of the lens in the eye leading to a decrease in vision (cataract)
- Numbness
- Blisters or sores in the mouth (stomatitis, mucositis)
- Low levels of potassium in the blood which can cause an abnormal heart rate and can cause an irregular heartbeat, which can be serious and life-threatening
- Low blood levels of magnesium which can cause weakness, muscle cramps, or irregular heartbeat
- Increased risk of bleeding (INR increased)
- Teary or watery eyes
- Painful red eyes
- Eye discharge
- Swelling of arms or legs (edema)
- Abnormal sensation such as pins and needles (tingling, burning)
- Eyelashes grow inward toward the eye. The lashes rub against the cornea (front part of eye), in conjunctiva (thin, clear, moist part that coats the inner surface of eyelids), the inner surface of the eyelids, or any abnormal or excessive growth
- Retinal disorders including damage to the retina leading to possible vision loss; Buildup of fluid at the back of the eye which may lead to impaired vision; separation of the retina from its connection at the back of the eye (retinal detachment); eye damage which may cause vision problems
- Low blood levels of phosphate which may cause muscle weakness, bone pain, confusion or muscle breakdown
- Decreased level of sodium in the blood (hyponatremia), which may cause headache, confusion, convulsions (seizure) and/or loss of consciousness (coma)
- Throat inflammation or pain (esophagitis)
- Troponin T increased (abnormal blood test), which may be a possible sign of heart problems
- Dehydration (lack of fluid in the body) – if severe it may require medication, IV fluids, and/or possibly hospitalization
- Shortness of breath (dyspnea)
- Abnormal electrocardiogram (ECG/EKG) – unusual heart rhythms
- Fever
- Slowed heart rate (sinus bradycardia) which can cause dizziness, faintness and tiredness
- Hives (urticaria) – swollen raised areas on the skin that are intensely itchy

- Blisters on the skin (bullous dermatitis) which may be severe
- Skin fissures – cracks in the skin which may bleed or be painful

Uncommon (≥0.1% and <1%) **or rare** (≥ 0.01% and < 0.1%) **and severe or significant possible side effects** have been reported

- Vague feeling of bodily discomfort or lack of energy (malaise)
- High blood pressure
- Increased risk of various infections [e.g., lung infection, bronchitis, nail infection, finger infection, mouth infection, throat infection (sore throat), skin infection] due to low white blood cell counts, decrease in immune system, or disruption of the mucous membrane
- Painful or abnormal sensations in the mouth
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing
- Fainting
- Urinary retention (unable to urinate)

Futibatinib has also been given to more than 816 people as of January 23, 2023. About 629 patients received futibatinib alone at a starting dose of 20 milligrams per day (478 patients) and the rest of the patients received futibatinib in combination with another drug. Possible side effects of futibatinib alone that affected cancer patients in the completed registration study for cholangiocarcinoma are included in the list above. Some of the possible side effects could be serious, life-threatening, or even fatal. Some side effects ma not disappear completely even after you stop taking futibatinib.

<u>For futibatinib in combination with pembrolizumab:</u>
Futibatinib has been given in combination with pembrolizumab to a total of 102 Japanese patients with different types of solid tumors and 37 Western patients with urothelial carcinoma as of January 23, 2023.

Possible side effects reported in patients taking futibatinib in combination with pembrolizumab (in addition to or more frequently than patients who took futibatinib alone) in at least 2 or more patients are listed below. Some of the possible side effects could be serious, life-threatening, or even fatal.

- Diarrhea
- Dry mouth
- Nausea
- Changes in taste
- Reduced desire to eat
- Inflammation of the mouth – blisters or sores
- A vague feeling of bodily discomfort (malaise) or lack of energy (asthenia)

- Underactive thyroid gland, which may cause possible weight gain, heart failure and/or constipation
- Swelling of arms or legs (edema)
- Lowered weight (weight loss)
- Itching (pruritis)
- Acne-like skin rash
- Dry skin
- Cracks in the skin that may bleed or be painful
- Separation of the retina from its connection at the back of the eye, which may cause partial blindness
- Swelling under the central part of the retina and possible loss of vision
- Tightening of the muscles in your arms or legs which may decrease the range of motion
- Increased blood level of an enzyme called creatine phosphokinase, which can be a sign of possible muscle damage or muscle breakdown
- Belly pain, feeling of fullness or tightness
- Dizziness
- Damage to liver cells
- Low levels of magnesium in the blood which may cause weakness, muscle cramps, and or irregular heart beat
- Kidney failure

In addition the following severe or significant possible side effects have been reported in one (1) patient each:

- Inflammation of the colon (colitis)
- Inability to fully empty your bladder (urinary retention)

Risks and Side Effects for Pembrolizumab

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way these organs work, which can result in side effects. These side effects may be serious (i.e., causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

VERY COMMON risks and side effects - Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON risks and side effects - Out of 100 people who receive pembrolizumab, at least 5 people but fewer than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color (vitiligo) – may lead to patchy appearance of the skin
- Not enough thyroid hormone(hypothyroidism) - you may feel tired, gain weight, feel cold, or have infrequent or hard stools
- Low levels of salt in the blood (hyponatremia) that may cause you to feel tired, feel confused, have a headache, have muscle cramps, or feel sick to your stomach

UNCOMMON risks - Out of 100 people who receive pembrolizumab, at least 1 but fewer than 5 people may have the following:

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, have a drop in your blood pressure while receiving your infusion (IV) or just after the infusion is done, or have pain at the site of the infusion
- Inflammation of the bowels or gut, which may cause severe pain in your belly with loose or watery stools, or black, tarry, sticky stools, or stools with blood or mucus (colitis)
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching, and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. Severe cutaneous adverse reactions or SCARs, include Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN))

RARE risks - Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the sheath that covers the nerves (Guillain-Barré syndrome) that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms, and upper body, leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles(myositis), so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls blood sugar levels) (pancreatitis), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and/or have vomiting that gets worse when you eat
- Inflammation of the eye (uveitis), so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches
- Inflammation of the liver (hepatitis) that may make you feel sick to your stomach and vomit, not feel like eating, feel tired, have a mild fever, have pain in the right side of your belly, have yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head) (hypophysitis), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting
- Adrenal glands (glands on top of the kidneys) may not make enough hormone (adrenal insufficiency), which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, or belly aches; nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 diabetes, a condition that can cause too much sugar in your blood – you may feel thirstier than usual, have frequent urination, and weight loss. If this type of diabetes occurs you are likely to need regular insulin shots
- Inflammation of the kidney (nephritis), so you may pass less urine or have cloudy or bloody urine, swelling, and low back pain
- Inflammation of the heart muscle (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting
- Inflammation of the thyroid gland (thyroiditis), an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)

- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain or spinal fluid (meningoencephalitis) with confusion and fever which may also include disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, headache, weakness or loss of movement in some parts of your body, and loss of consciousness
- Inflammation of the spinal cord with pain (myelitis), numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, or constipation
- Inflammation of the blood vessels (vasculitis) - symptoms will depend on which blood vessels are involved in the inflammatory process, for example, if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin, and brain. These responses may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes.
- Hemophagocytic lymphohistiocytosis (HLH) including macrophage activation syndrome (MAS) - life-threatening hyper-inflammatory disorder that attacks multiple organs at once
- Changes in eyesight, eye pain, whitish patches on the skin, and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This scarring can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Immune-mediated pericardial disorders including pericarditis, pericardial effusion and cardiac tamponade (buildup of fluid in the sac surrounding the heart)

Risks related to pregnancy
You should not become pregnant or father a baby while you are receiving futibatinib and for 90 days after your last dose of futibatinib. Chemotherapy can cause harm to an unborn child. If you are pregnant, trying to become pregnant or breast-feeding, you may not be in the study. The

study doctor will perform a pregnancy test before the start of and during the study, if you are able to have a baby. If the test is positive, you will not be able to be in the study.

In animal studies, futibatinib caused low body weight of the fetus and caused birth defects at a dose lower than the current clinical dose; at higher doses than the current clinical dose, futibatinib induced death of the fetus.

Based on findings from animal studies, futibatinib can cause fetal harm when administered to someone who is pregnant. If you are able become pregnant or father a child you must agree to use an effective method of birth control during the trial and for 90 days after your last dose of futibatinib. Your doctor will discuss the most effective methods of birth control with you.

If you think that you or your partner might be pregnant, you must immediately inform your study doctor.

Biopsies
Biopsies are normally performed under the guidance of an imaging technique such as CT or ultrasound. Each procedure requires a separate consent prior to the biopsy. If you are able to become pregnant, you must have a pregnancy test prior to the biopsy.

The risks of biopsies may include:

- Pain and discomfort -The amount of pain and discomfort will vary, depending on the location of the biopsy site
- Minor bleeding at the biopsy site
- Tenderness at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These complications might require additional surgical intervention.

Radiation Risk
You will be exposed to radiation if CT is used to perform the biopsy. The amount of radiation has a low risk of harmful effects.

If you are able to become pregnant, you must have a pregnancy test prior.

Standard of Care Risks
Your doctor will discuss the risks of these tests and procedures, which are part of regular care for your cancer:

- Treatment with pembrolizumab
- Imaging of your cancer (CT, MRI, etc.)

Blood draws
The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

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

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

All health insurance companies and group health plans must follow this law.

Be aware that this new Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Risks Associated with Genomic Testing
This study involves testing your DNA, which is the genetic information you inherited from your parents (also known as genetic testing). This testing may include whole genome sequencing (mapping your entire genetic code). You will not be notified of the genetic test results and they will not be put into your medical record.

Despite the GINA protections and the best efforts of the research team, there may still be a risk if information about you were to become known to people outside of this study.

Genetic information is unique to you, even without your name or other identifiers. For this reason, genetic information like DNA may be used to identify you and possibly your family members. We have procedures (such as, labeling your biospecimens with a password protected code known only to select research staff) to prevent people working with your DNA from discovering if it belongs to you. However, there is the risk this can happen as new ways of tracing genetic information are being developed that may make re-identification of genetic information possible.

Confidentiality Risk
As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Unforeseeable Risks
Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell your study doctor if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the study doctor; the study sponsor, Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you don't follow the study procedures,
- If the study is stopped,
- For administrative reasons, including competitive enrollment.

If any new information becomes available that may be relevant to your willingness to continue participation in this research study, the study team will inform you in a timely manner.

If you choose to withdraw from this clinical trial, your original consent to data or sample processing is still valid. Any results obtained from testing of your samples can still be used by the Sponsor (Mayo Clinic). However, no other new samples will be collected, and you may also

request that no new analyses be performed after withdrawal. If you decide at any time during the period of the trial that you want any of your submitted samples withdrawn, you will need to contact your study doctor in writing, who will then contact the laboratory to have your samples destroyed. However, any results already obtained from testing of your samples can still be used.

What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance. The study will not offer free medical care or payment for any bad side effects from taking part in this study.

What are the possible benefits from being in this research study?

This study may not make your health better. However, others with liver cancers may benefit in the future from what we learn in this research study.

What alternative do you have if you choose not to participate in this research study?

You don’t have to be in this study to receive treatment for your condition. Your other choices may include: treatment for your cancer without being on a study, treatment on a different research study, or no treatment. Talk to the Principal Investigator or your doctor if you have any questions about any of these alternative treatments or procedures.

What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Research biopsy prior to starting this study
- Research testing on blood and tissue

The study drug, futibatinib, will be given to you at no cost. You and/or your insurance might also have to pay for other drugs or treatments given to help control side effects.

You and/or your insurance will need to pay for all other tests and procedures that are part of this research study and/or needed for your clinical care including copayments and deductibles. These costs include the cost of pembrolizumab and the costs to administer pembrolizumab.

Before you take part in this study, you should call your insurer to find out if the cost of these tests and/or procedures will be covered. You will have to pay for any costs not covered by your insurance.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

Will you be paid for taking part in this research study?

You will not be paid for taking part in this study.

There is a very small chance that some commercial value may result from the use of your donated samples. This could include new products like a drug or a test to diagnose a disease. If that happens, you won't be offered a share in any profits.

Will your information or samples be used for future research?

Your information and samples will be kept by the Sponsor, Mayo Clinic. Mayo Clinic can use your data and samples for research purposes only as described in the research study. Your data and samples will be sent to the Mayo Clinic in a coded format, which protects your identity. Mayo Clinic may destroy the samples at any time without telling you. We will test your tissue and blood as part of this study. In addition, we would like to keep your study information and samples for future research. You can still take part in this study without giving permission to use your data and samples for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity. Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). If there are findings which may be useful for your health care, the researchers may contact Mayo Clinic, so Mayo Clinic can give you the option of learning the results. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

To support future research, de-identified genetic information may be placed in databases accessible by the internet. Some of the information may be available to anyone using the internet, and some will be released only to approved researchers. Combined study information (including genomic summary results) may be published, but the information will not identify you.

Even though information traditionally used to identify you will not be shared, people may develop ways in the future to allow someone to link your genetic information back to you. For this reason, confidentiality cannot be guaranteed. It is also possible that re-identified information could be used in discriminating ways, and there could be additional unknown risks. We will make every effort to protect your confidentiality.

Approval Date: **March 13, 2024**
Not to be used after: **March 12, 2025**

Please read the following statements and mark your choices:

I permit my information and samples to be stored and used in future research to learn about, prevent or treat cancer:

☐ Yes ☐ No Please initial here: _____Date: _____

I permit my information and samples to be stored and used in future research to learn about, prevent, or treat any other health problems (for example: causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism):

☐ Yes ☐ No Please initial here: _____Date: _____

I permit Mayo Clinic to give my samples to researchers at other institutions:

☐ Yes ☐ No Please initial here: _____Date: _____

I agree to have my coded genetic information and coded medical information placed in password-protected secured databases for research analyses.

☐ Yes ☐ No Please initial here: _____Date: _____

I agree that my study doctor, or someone on the Mayo Clinic study team, may contact me to see if I wish to participate in other research in the future.

☐ Yes ☐ No Please initial here: _____Date: _____

You may withdraw your consent for future use of your information and/or samples at any time, by writing to the Principal Investigator at the address provided in the "Contact Information" section of this consent form.

Your information and/or samples would be removed from any repository where they are stored, if possible. Information and/or samples already distributed for research use will not be retrieved. Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

It is possible that information identifying your samples or your data could be removed. These samples and data will no longer be linked to you. If that were to happen, the samples and data could be used for future research studies or given to another researcher without asking for your permission.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. All of your research samples transferred to the Mayo Clinic or designee will be labeled with a code number and kept in locked storage. Only your study doctor will be able to link your samples with your identity. No one working with your samples will know your identity. If the results of the research are made public, information that identifies you will not be used.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Your health information may be collected from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- Researchers involved in this study at other institutions.
- The sponsor of this study, Mayo Clinic, and the people or groups hired by the sponsor(s) to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.

- National Comprehensive Cancer Network (NCCN), the funding organization for this study through a grant fromTaiho Oncology, Inc.
- Taiho Oncology, Inc, the provider of the study drug, futibatinib (TAS-120)
- A group that oversees the data (study information) and safety of this research.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.

If the results of this study are made public (for example, through scientific meetings, reports or media), information that identifies you will not be used.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying ‘no’ will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Plummer Building PL 3-02
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Participant Advocate at: researchparticipantadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts forever, unless you cancel it.

Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature