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Brief Title: A Trial of NIS793 With FOLFIRINOX in Pancreatic Cancer

Full Title: A Phase 2 study of neoadjuvant NIS793 in Combination with mFOLFIRINOX in resectable and borderline resectable pancreatic adenocarcinoma (PDAC)

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Protocol Title: A Phase II study of neoadjuvant NIS793 in Combination with mFOLFIRINOX in resectable and borderline resectable pancreatic adenocarcinoma (PDAC)

DF/HCC Principal Investigator / Institution:

Kimberly Perez, MD / Dana-Farber Cancer Institute

Main Consent

INTRODUCTION AND KEY INFORMATION

All research is voluntary. It is your choice whether you take part in this research or not. If you decide to participate, please sign and date at the end of this form. We will give you a copy and you can refer to this consent form at any time.

The following is a short summary of this research study to help you decide whether you would like to be a part of this study. More detailed information is provided later in this form.

For purposes of this research, you will be referred to as a "participant."

1. Why am I being invited to take part in a research study?

You are invited to take part in this research study because you have pancreatic cancer.

2. Why is this research being done?

This study is being done to evaluate the safety and efficacy of adding NIS793 to standard of care neoadjuvant mFOLFIRINOX.

3. Who is supporting this research?

The sponsor of this trial is Dana-Farber/Partners Cancer Care on behalf of the Dana-Farber/Harvard Cancer Center (DF/HCC). Novartis Pharmaceuticals Corporation is supporting this research study by providing the study drug NIS793.

4. What does this research study involve and how long will it last?

This research study involves immunotherapy. Immunotherapy triggers the body's immune system to fight cancer cells.

The names of the study interventions involved in this study are:

- NIS793

- FOLFIRINOX (Folinic acid/Leucovorin, 5-Fluorouracil, Irinotecan, and Oxaliplatin)
- Capecitabine
- Chemoradiation Therapy

The research study procedures include screening for eligibility and study treatment including evaluations and follow up visits.

You will receive study treatment as long as your disease does not worsen, or you do not have serious side effects for a maximum of 8 cycles (16 weeks).

It is expected that about 45 people will take part in this research study.

Information about you and your health is personal and private. Generally, it cannot be obtained without your written permission. By signing this form, you are providing that permission and your information may be obtained and used in accordance with this informed consent and as required or allowed by law. This means that researchers may obtain information regarding your past medical history, as well as specimens and samples from previous health care providers such as hospitals and labs.

5. What are the risks to participating in this study?
There are risks to taking part in any research study. We want to make sure you know about a few key risks right now. There may also be rare, serious and potentially life-threatening side effects. More detailed information is provided in the “What are the risks or discomforts of the research study?” section.

There is a risk that you could have side effects from NIS793 and mFOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan). These side effects may be worse and may be different than you would get with other approaches for your cancer.

Some of the most common side effects that the study doctors know about are:

- Fatigue
- Vomiting
- Diarrhea
- Abdominal pain
- Swelling and redness of the skin
- Fever
- Mouth sores
- Temporary changes in blood work, which may include the following:

- Low number of red blood cells that can cause tiredness and shortness of breath. This condition may require a blood transfusion.
- Abnormally low number of white blood cells called neutrophils. This increases the risk of infection, which may be serious or life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion.

Side effects from the study treatment might result in a delay or prevention in your ability to undergo standard of care treatment, including surgery.

In addition to the above, there may be other side effects that may happen that are not known now.

6. Will being in this study benefit me in any way?

We do not know if taking part in this study will benefit you. This study may help researchers learn information that could help people in the future.

7. What are my options?

Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment such as chemotherapy using fluorouracil, leucovorin, irinotecan and/or oxaliplatin, but not as part of a research study.
- Receive standard treatment such as chemoradiation therapy.
- Decide not to participate in this research study.
- Participate in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions at any time.

A. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational drug to learn whether the drug works in treating a specific disease. "Investigational" means that the drug is being studied.

The U.S. Food and Drug Administration (FDA) has not approved NIS793 as a treatment for any disease.

In this research study, we are combining standard chemotherapy used for localized pancreatic cancer called FOLFIRINOX with an investigational agent, NIS793. This new medicine, NIS793, blocks a molecule called TGF-beta. TGF-beta has been shown to promote the growth of pancreatic cancer and our hope is that blocking this will allow the chemotherapy to work better against the cancer.

B. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Patients will be randomly assigned to one of the two groups, called "arms":

Arm A will receive standard chemotherapy, mFOLFIRINOX, in combination with NIS793.

Arm B will receive standard chemotherapy, mFOLFIRINOX.

If the study team believes chemoradiation would benefit you, then you will be offered to receive chemoradiation following completion of chemotherapy.

If the study team believes surgery would benefit you, then you will be offered to undergo surgery following either completion of chemotherapy or chemoradiation, dependent upon your staging scans.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Clinical Exams,** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions

about any problems that you might be having and any medications you may be taking.
- **Vital signs**
- **Height and weight**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An assessment of your tumor** by one or more of the following standard assessment tools: CT (Computerized Tomography) scan or MRI (Magnetic Resonance Imaging).
- **Blood tests for routine testing,** a maximum of approximately 4 teaspoons of blood will be collected.
- **Urine or Serum pregnancy test,** if you are able to become pregnant.
- **Biopsy** a mandatory biopsy of your tumor will be collected to confirm your cancer diagnosis. If a biopsy has already been performed, an additional pretreatment biopsy of your tumor will not be mandatory. If the results from your previously performed biopsy are unclear, your doctor might need to obtain your previously collected and stored tissue (archival tissue) for further testing or have you perform an additional biopsy.
- **Electrocardiogram (EKG), Echocardiogram (Echo), or cardiac CT/MRI,** which records the electrical activity and function of your heart

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Additional research procedures to be performed at the time of screening but not required to determine eligibility:

- **Blood tests**, including baseline tests so that we can measure any additional effect of the study drug and disease status or to look for a marker for your particular type of cancer.
- **HIV tests:** You will have blood samples (less than 1 tablespoon) taken to test for HIV (human immunodeficiency virus). The purpose of this routine laboratory test is to determine whether the virus that is associated with Acquired Immune Deficiency (AIDS) that harms the immune system is present in your blood. The results of these tests will appear in your medical record and will be shared with health care workers involved in your care. The test results will be shared with the study supporter(s) to perform functions relating to the conduct of this research. All positive results will be shared with a health authority (e.g., the State Department of Health) as required by law.

- **Biobanking:** Biological specimens (such as blood and tissue) will be collected and shared with an outside lab or collaborator for analysis. If you have had a biopsy, we will ask the pathology department at the hospital where you had your biopsy to share some of the specimens (archival tissue) that was used for diagnosis. The specimens will not be identifiable. The specimens will be banked for future use.
- **Data Collection:** Data will be collected and shared with an outside collaborator for analysis. The data will be stored identifiable and will be de-identified if ever shared. The data will be banked for future use.
- **Optional Studies:** You will be asked if you want to participate in any optional research. The optional research is described in Section Q. You do not have to agree to participate in the optional studies to participate in the main study.

Study Treatment Overview:

- **Infused Study Drugs**

  NIS793: each study treatment cycle lasts 14 days during which you will receive study drug into your vein (by intravenous infusion) over about 30 minutes. This will continue for up to 8 cycles.
  Leucovorin and Oxaliplatin: each study treatment cycle lasts 14 days during which you will receive study drug into your vein (by intravenous infusion) over about 120 minutes. This will continue for up to 8 cycles.
  Irinotecan: each study treatment cycle lasts 14 days during which you will receive study drug into your vein (by intravenous infusion) over about 90 minutes. This will continue for up to 8 cycles.
  Fluorouracil: will be given once every 14 days into your vein (by intravenous infusion) over about 46 hours. This will continue for up to 8 cycles.

- **Oral Study Drug**

  Capecitabine: study drug will be taken on the days of chemoradiation.

- **Pre-medications:** You may be pre-medicated with drugs to reduce the chance of having a sensitivity reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor.

Study Visit: Day 1 of each Cycle of Chemotherapy

- **Clinical Exams***:* During this visit you will have a physical exam and you will be asked questions about your general health and specific questions

about any problems that you might be having and any medications you may be taking.
- **Vital signs**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests for routine testing (approximately 1 tablespoon of blood)**
- **Blood tests for exploratory research (approximately 2 tablespoons of blood)**
- **Infused Study Drugs** FOLFIROX (Group A and B) or NIS793 (Group A)
- **Electrocardiogram (EKG), Echocardiogram (Echo), or cardiac CT/MRI,** which records the electrical activity of your heart (Group A)

Study Visit: Every 8 weeks during chemotherapy
- **Scans (or Imaging tests):** We will assess your tumor by CT or MRI scan.
- **Optional Studies:** You will be asked if you want to participate in any optional research. The optional research is described in Section R. You do not have to agree to participate in the optional studies to participate in the main study.

Study Visit: Day 1 of each radiation therapy
- **Radiation therapy**
- **Oral Study Drugs** Capecitabine
- **Infused Study Drugs** Fluorouracil
- **Clinical Exams***:* During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Vital signs**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests for routine testing (approximately 1 tablespoon of blood)**
- **Blood tests for exploratory research (approximately 2 tablespoons of blood)**

Study Visit: Surgery
- **Clinical Exams***:* During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Vital signs**

- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests for routine testing (approximately 1 tablespoon of blood)**
- **Blood tests for exploratory research (approximately 2 tablespoons of blood)**
- **Surgery**

Study Visit: End of Treatment

- **Clinical Exams*:*** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Vital signs**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests for routine testing (approximately 1 tablespoon of blood)**
- **Blood tests for exploratory research (approximately 2 tablespoons of blood)**

Study Visit: Follow-up visits once every 12 weeks

- **Clinical Exams*:*** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Vital signs**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests for routine testing (approximately 1 tablespoon of blood)**
  Blood tests for exploratory research (approximately 2 tablespoons of blood)
- **Scans (or Imaging tests):** We will assess your tumor by CT or MRI scan.

Research Study Plan:

	Visit 1	Visit 2	Every 2 weeks	Every 4 weeks	Every 8 weeks	Radiation Therapy	Surgery	End of treatment	Follow-up Visits
	Screening	Day 1							
Medical History & Physical Exam	X	X	X			X	X	X	X
Performance Status and Vitals	X	X	X			X	X	X	X
Height	X								
Blood Test	X	X	X			X	X	X	X
Research Blood Draw	X	X	X			X	X	X	X
Archival Tissue Collection	X								
CT or MRI Scan	X				X	X	X		X
Tumor Biopsy	X						X[3]		
Pregnancy Test[1]	X	X		X		X	X	X	X
EKG (Group A)	X	X	X						
Echocardiogram or Cardiac CT/MRI (Group A)	X		X[2]						
Receive Study Drugs NIS793 and/or FOLFIRINOX		X	X						
Receive Study Drugs Capecitabine OR Fluorouracil						X			
Optional Biopsy for Research	X							X	

[1] For women of childbearing potential
[2] Repeated only if clinically indicated and/or if cardiac enzymes are elevated
[3] A biopsy of your tumor for research during your surgical procedure will only occur if we cannot collect a sample of your tumor from your surgery and your surgeon determines it safe to perform the biopsy.

Planned Follow-up:

We would like to keep track of your medical condition. After your last dose of the study, we would like you to come in for follow up visits every 12 weeks after you

stop taking the study drugs. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal not be removed from the study.

C. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study drug combination that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with NIS793:

Occasional (Between a 1-10% chance that this will happen)

- Allergic reaction

- The study drug may cause cytokine release syndrome. This involves a release of a large amount of proteins into the blood stream. This may cause changes in blood pressure and heartbeat, flu-like symptoms (nausea, fever, and chills), and/or affect your lung/liver/kidney function. It may also cause certain brain-related symptoms, such as dizziness, weakness, confusion, difficulty speaking, and/or decreased brain function (possible paralysis and/or coma).Heart damage
- Skin rash
- Bleeding or bruising
- Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion.
- Abnormally low number of white blood cells called neutrophils that can increase the risk of infection. May be serious or life-threatening.
  - Symptoms of infection may include fever, pain, redness, and/or difficulty breathing
- Low number of platelets which may cause bleeding and bruising. Bleeding may be serious or life-threatening and may require a blood transfusion.
- Decreased kidney function
- Eye pain, visual disturbances, and changes in color perception
- Liver test abnormalities
- Bone pain
- Fatigue
- The study treatment may cause you to develop another type of skin tumors, specifically keratoacanthomas and squamous cell carcinomas

Risks Associated with Fluorouracil:

Frequent (Between a 11-50% chance that this will happen)

- Sickness
- Vomiting
- Mouth sores
- Diarrhea
- Abdominal pain
- Tiredness
- Swelling and redness of the skin
- Fever

Occasional (Between a 1-10% chance that this will happen)

- Itching, peeling, and/or pain of the skin of the hands and feet
- Diminished appetite
- Loss of hair

- Dizziness
- Chest pain due to heart trouble
- Heart attack and change of heart rhythm
- Confusion
- Mood swings
- Watering of the eyes due to excessive tear production
- Fatigue
- Weakness
- Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion.
- Abnormally low number of white blood cells called neutrophils that can increase the risk of infection. May be serious or life-threatening.
  - Symptoms of infection may include fever, pain, redness, and/or difficulty breathing
- Low number of platelets which may cause bleeding and bruising. Bleeding may be serious or life-threatening and may require a blood transfusion.

Risks Associated with Leucovorin:

Occasional (Between a 1-10% chance that this will happen)

- Allergic reaction
- Rash
- Itching
- Facial flushing
- Nausea
- Vomiting

Risks Associated with Irinotecan:

Frequent (Between a 11-50% chance that this will happen)

- Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion.
- Abnormally low number of white blood cells called neutrophils that can increase the risk of infection. May be serious or life-threatening.
  - Symptoms of infection may include fever, pain, redness, and/or difficulty breathing
- Low number of platelets which may cause bleeding and bruising. Bleeding may be serious or life-threatening and may require a blood transfusion. Loss of appetite
- Mild diarrhea
- Mild fatigue
- Sores in the mouth and throat
- Cardiovascular events such as a fast or irregular heartbeat

- Hair loss
- Abnormal liver test values
- Decreased kidney function
- Nausea and vomiting
- Constipation
- Pain

Occasional (Between a 1-10% chance that this will happen)

- Severe diarrhea
- Bleeding that may require a blood transfusion
- Moderate fatigue
- Infection

Rare (Less than a 1% chance that this will happen)

- A serious decrease in blood counts that could result in infection, a need for blood transfusion, or a need for a platelet replenishment
- Liver failure that may lead to death
- Kidney failure that may lead to death or the need for dialysis
- Heart attack
- Stroke
- High blood pressure

Risks Associated with Oxaliplatin:

Frequent (Between a 11-50% chance that this will happen)

- Nerve damage (possible numbness, pain, and/or loss of motor function), especially in the case of cold exposure, and an unusual feeling of numbness of the mouth and throat that may cause difficulty in swallowing and can be made worse by cold water or drinks. This nerve damage can cause the following:
  - This is a sensation of pain when you are exposed to cold, either by touch, or by eating/drinking something cold. Do not eat or drink anything that is colder than room temperature for five days after you receive each dose of oxaliplatin.
  - Decrease in feeling or funny feeling in the hands, feet and mouth or throat that can interfere with daily activities (writing, buttoning, swallowing, and walking). This may worsen over time.
- Jaw spasm
- Abnormal tongue sensation
- Difficulty speaking
- Eye pain
- Feeling of chest pressure

- Fatigue
- Nausea
- Vomiting
- Diarrhea

Occasional (Between a 1-10% chance that this will happen)

- Mouth sores
- Hair loss
- Temporary loss of hearing
- Disturbances of kidney function
- Reduced reflexes
- Skin rash
- Fever
- Fainting
- Tissue scarring of the lung
- Severe allergic reaction and mild to moderate swelling and redness at the injection site
- A feeling of tightness or tingling in the throat
- Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion.
- Abnormally low number of white blood cells called neutrophils that can increase the risk of infection. May be serious or life-threatening.
  - Symptoms of infection may include fever, pain, redness, and/or difficulty breathing
- Low number of platelets which may cause bleeding and bruising. Bleeding may be serious or life-threatening and may require a blood transfusion. Bleeding or bruising
- Increase in the value of liver enzymes

Risks Associated with Capecitabine:

Frequent (Between a 11-50% chance that this will happen)

- Swelling
- Fatigue
- Hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering)
- Skin irritation, rash
- Diarrhea
- Nausea
- Vomiting
- Abdominal pain

- Mouth blisters/sores
- Decreased appetite
- Lowering of white blood cells called neutrophils that can increase the risk of infection. May be serious or life-threatening.
  - Symptoms of infection may include fever, pain, redness, and/or difficulty breathing
- Low number of red blood cells that can causes tiredness and shortness of breath. May require a blood transfusion.
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life-threatening and may require a blood transfusion.
- Abnormal liver tests (possible yellowing of the skin and/or eyes)
- Elevation of liver tests
- Abnormal sensation (such as pins and needles)
- Eye irritation

Occasional (Between a 1-10% chance that this will happen)

- Blood clots in a vein (possible pain, swelling, and/or redness)
- Chest pain
- Headache
- Dizziness
- Difficulty sleeping
- Mood alteration, depression
- Nail changes
- Change of skin color
- Hairloss
- Redness of the skin
- Dehydration
- Gastrointestinal digestive disorders
- Oral discomfort
- Abnormal taste
- Heartburn
- Digestive system bleeding
- Paralysis of the intestines
- Neuromuscular and skeletal: back pain, weakness, nerve damage, muscle pain, joint pain, limb pain
- Abnormal vision
- Painful red eyes
- Cough

Risks Expected after Radiation:

Likely (More than a 50% chance that this will happen)

- Fatigue (which generally goes away after the radiation therapy is completed)
- Temporary changes in blood work (decreases in blood counts, increases in liver enzymes), without symptoms

Frequent (Less than 30% chance that this will happen)

- Nausea
- Vomiting (during therapy)
- Skin irritation, redness, itchiness, discomfort

Rare (Less than a 5% chance that this will happen)

- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (< 10% permanent changes)
- Radiation-induced liver disease (RILD) (<1%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~5%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.
- Diabetes (<1%)
- Cancer caused by radiation (<0.1%)

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Risks Associated with Biopsies:

Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- 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 might require additional surgical intervention.

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans, PET/CT scans, Bone Scans, x-rays, mammograms, and/or other scans utilizing radioactivity may be used to evaluate your disease.

In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Certain types of drugs or combinations of these drugs with radiation may further slightly increase the risk of developing a new cancer.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the CT scan or MRI scan. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus.
While participating in this research study and for 120 days after last study treatment, you should not:

- become pregnant
- nurse a baby
- father a baby

We can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

If your partner becomes pregnant while you are on the study, it may be critical to share information regarding your participation in this research study with that person. Your research doctor should also be told if this happens.

Risks of Tissue Collection for Biobanking:
Generally, hospitals will keep some of your tissue. There is a small risk that when this tissue is collected and the sample is submitted to the biobank, your tissue could be used up and unavailable for use in the future.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

D. WHAT WILL HAPPEN IF I AM REMOVED FROM THE STUDY OR DECIDE TO END MY PARTICIPATION IN THE RESEARCH?

You may be taken off the research study for any reason including:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- If you have any problems following study treatments and procedures
- You become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to end the study

- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

You can also choose to stop participating in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study drugs. In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

It is important to note that although you may withdraw from study participation, the FDA requires that any information collected up to the point of your withdrawal not be removed from study records. Additionally, the research doctor may consult public records after you have withdrawn from the study.

If you agree to allow your blood or tumor tissue to be kept for future research with identifying information that could link your sample to you, you may withdraw your permission at any time. We ask that you contact your study doctor and let them know you are withdrawing your permission for your identifiable blood or tumor tissue to be used for future research.

E. WHAT ARE THE BENEFITS OF THIS RESEARCH STUDY?

Taking part in this research study may or may not benefit you. We hope the information learned from this research study will provide more information about different treatment options for pancreatic cancer. Participating in this study may result in your cancer being controlled for longer than it would have on standard of care drugs. The knowledge gained from the research will help medical personnel be able to better treat other people diagnosed with pancreatic cancer in the future.

F. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor-investigator and hospital may benefit if this happens. There are

no plans to pay you if your samples are used for this purpose.

G. WHAT ARE YOUR COSTS?

Taking part in this research study may lead to added costs to you or your insurance company. This may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your disease. You may:

- Have more travel costs
- Need to take more time off work
- Have other additional personal costs

You will not be charged for NIS793.

It is possible that NIS793 may not continue to be supplied free for some reason. If this would occur, your research doctor will talk with you about your options.

You or your insurance company will be charged for portions of your care during this research study that are considered standard of care, fluorouracil, leucovorin, irinotecan, and oxaliplatin. Standard of care is the care that you would receive regardless of whether you were enrolled in the study or not. You may be responsible for co-payments, co-insurance, premiums and deductibles that are typical for your insurance coverage. This includes the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests, done for research only, are supplied at no charge.

You or your insurance company will be charged for portions of your care during this research study that are considered routine costs. Routine costs ***may*** include services to determine your eligibility, services to prevent (monitor) and diagnose disease, and services to treat side effects. Examples of research study routine costs may include the infusion of the study medicines, office visits, lab tests, procedures, and imaging.

You may be billed for co-payments, co-insurance, premiums and deductibles that are typical for your insurance coverage. Participation may result in additional ***routine costs*** because of more frequent research visits.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Dana-Farber Cancer Institute: (617) 632-3455

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov
or 1-800-4-CANCER (1-800-422-6237)

H. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments may be billed to you or your insurance company. You will be responsible for deductibles, co-payments and co-insurance. There are no plans to pay you or give you other compensation for the injury.

You do not give up any of your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in this research. If possible, you should give them a copy of this consent form.

I. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Dana-Farber Cancer Institute

- Kimberly Perez, MD: (617) 632-6491
- 24-hour contact: call 617-632-3352 and ask for your treating oncologist or the doctor on call to be paged

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

J. RETURN OF RESEARCH RESULTS

Tests done on samples in this research study are only for research and have no clear meaning for your health care. For this reason, your study doctor will not share the results with you.

K. CLINICALTRIALS.GOV

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.

L. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. Any personal identifiers will be removed, before they are shared, so that the information or samples cannot be linked back to you. As a result, we will no longer be able to identify and destroy them.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your de-identified information or samples in future research.

Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research, if the samples

and specimens are de-identified. There is a risk that you might be reidentified in the future as genetic research progresses

This protocol also involves optional research regarding the future use of specimens and/or data. Please refer to section R for more information regarding this optional research, and to indicate whether or not you'd like to participate.

M. CONFIDENTIALITY

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. It may also become part of a research database.

Participation in this study involves providing a specimen of your tissue; please know that if the research doctor leaves the institution, the research and the tissue might remain at the research doctor's current institute or might be transferred to another institution.

The study team may publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

Your de-identified specimens or genetic data may also be placed into one or more publicly-accessible scientific databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research.

There is a risk that de-identified research data that is shared with outside collaborators may be reidentified. When de-identified data and specimens are shared with outside collaborators agreements limit what the outside collaborators can do with the information to help prevent reidentification.

N. FINANCIAL DISCLOSURES

It is possible that certain researchers on this study may have earned money from, or own some publicly-traded stock in, the company that makes or is developing the study drug. The amount of money that a researcher may earn and

still take part in research is limited by the Harvard Medical School Faculty of Medicine Policy on Conflicts of Interest and Commitment. If you have further questions, please speak with a member of the study team or contact the Dana-Farber Cancer Institute Office of Research Integrity at 617-432-4557 or researchintegrity@dfci.harvard.edu.

O. GENETIC RESEARCH

This research will involve genomic and germline testing.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health, and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328.

As part of this study, your de-identified specimens or genetic data may be placed into one or more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). Through such databases, researchers from around the world will have access to de-identified samples or data for future research.

P. PRIVACY OF PROTECTED HEALTH INFORMATION (HIPAA AUTHORIZATION)

The Health Insurance Portability and Accountability Act (HIPAA) is a federal law that requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.

- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor-investigator with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).

- The supporter(s) of the study, its subcontractors, representatives, business partners, and its agent(s): Dana-Farber Cancer Institute, Novartis Pharmaceuticals Corporation, and MD Anderson Cancer Center
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- 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 treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

Q. CONSENT TO OPTIONAL RESEARCH STUDIES:

You are being asked to participate in some optional studies. If you decide not to participate in any of the optional studies, you can still participate in the main research study. Please take your time to make your decision and discuss it with others and your primary care physician.

Your participation in these optional research studies is voluntary, and you will not be penalized or lose any benefits if you refuse to participate or decide to stop.

Optional Study #1: Pretreatment Biopsy

We would like to collect a sample of your tumor before you start treatment so we can look at its characteristics before the treatment you will receive changes it. Your tumor sample will be stored in our biobank for future testing at Dana-Farber and Harvard Medical School. When stored in our biobank, your sample will be de-identified so that only the research team at Dana-Farber can identify that it belongs to you.

We would like to collect your tissue in one of the following ways.

1. If your doctor has determined that you will need to perform a biopsy to confirm your cancer diagnosis, we would like to collect additional samples of your tumor during that biopsy.
2. If you're no longer required to perform a biopsy to be eligible for this study, we would like to collect a sample of your tumor by performing an additional biopsy during the screening period that will only be done to collect samples for research.

Please see section C (Page 17) for the risks associated with biopsies.

You will **not** receive any additional fees if you choose to partake in this optional study. Your decision regarding participating in this optional study will **not** affect your ability to participate in the clinical trial.

Please indicate whether or not you want to take part in this optional research study.

☐ Not applicable

☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

Optional Study #2: Off Study Treatment Biopsy

If you or your study doctor decides to discontinue your study treatment before your surgery, we would like to perform a biopsy of your tumor. We will use this biopsy sample of your tumor to learn about how your cancer responded to the treatments you received. Your tumor sample will be stored in our biobank for future testing at Dana-Farber and Harvard Medical School. When stored in our biobank, your sample will be de-identified so that only the research team at Dana-Farber can identify that it belongs to you.

Please see section C (Page 17) for the risks associated with biopsies.

You will **not** receive any additional fees if you choose to partake in this optional study. Your decision regarding participating in this optional study will **not** affect your ability to participate in the clinical trial.

Please indicate whether or not you want to take part in this optional research study.

☐ Not applicable

☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

DFCI Protocol Number: 22-314	Approved Date (DFCI IRB Approval): 05/02/2023
Date Posted for Use: 05/19/2023	

R. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

_____ _____

Signature of Participant or Legally Authorized Representative — Date

_____

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

☐ *As someone who understands both English and the language used by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.*

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate