Cover Page

Official Title: A Phase 1b and Pharmacodynamic Study of Nintedanib Monotherapy Followed by Combination Therapy of Nintedanib and Gemcitabine Plus nab-Paclitaxel for Advanced Pancreatic Cancer

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CONSENT TO PARTICIPATE IN RESEARCH

Treatment Consent

Title of Research:	A Phase 1b and Pharmacodynamic Study of Nintedanib Monotherapy Followed by Combination Therapy of Nintedanib and Gemcitabine Plus nab-Paclitaxel for Advanced Pancreatic Cancer
Sponsor:	UT Southwestern Medical Center with funding support from Boehringer Ingelheim Pharmaceuticals, Inc.
Study Doctor:	Salwan Al Mutar, MD

You may call the study doctor or research personnel during regular office hours at 214-648-4180. At other times, you may call them at 214-645-4673.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
This study is being done to find out whether an oral investigational drug (non-FDA approved), Nintedanib (a tyrosine kinase inhibitor) taken alone, and in combination with gemcitabine plus nab-Paclitaxel (standard of care chemotherapy) will work better to decrease the blood supply to your tumor -- causing the tumor to shrink.

As your tumor grows it activates blood vessel growth (angiogenesis) by secreting growth factors that are important in the growth process. Therefore, the researchers believe that discontinuing the growth process with a tyrosine kinase inhibitor like, Nintedanib, in combination with standard chemotherapy is thought to be more effective than using a tyrosine kinase inhibitor alone or using the standard therapy alone.

Why is this considered research?
This is a research study because the combination of Nintedanib with gemcitabine plus nab-Paclitaxel has not been previously used in combination for metastatic pancreatic carcinoma. Although, Nintedanib is approved by the U.S. Food and Drug Administration (FDA), it is an investigational drug and has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced pancreatic cancer.

- Gemcitabine plus nab-Paclitaxel has been approved by the FDA as the standard treatment for advanced pancreatic cancer and is not considered an investigational treatment;
- Nintedanib with gemcitabine plus nab-Paclitaxel is being compared to gemcitabine plus nab-Paclitaxel alone, the standard treatment for your cancer, which has already been approved by the FDA. The researchers are interested in learning which therapy is more effective and/or safer in treating your tumor.

The following definitions may help you understand this study:

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center and its affiliated hospitals.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you have advanced pancreatic cancer.

Do I have to take part in this research study?
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?
About 20 people will take part in this study at UT Southwestern Medical Center

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this research study.

Screening Procedures (1 or 2 Days)
To help decide if you qualify to be in this study, the researchers may ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures that must be completed 21 days prior to registration:

- Completion of Informed Consent (Research Procedure)
- Collection of your demographics (age, gender, race) (Research Procedure)
- Review of your past and present medical history (Standard of Care procedure)

- Review of any medications that you are taking or have taken (Standard of care procedure)
- Review of any side effects that you may have experienced (Adverse Events) assessment (Research procedure)
- Physical Exam (PE) (Standard of Care procedure)
- Height and weight (Standard of care procedure)
- ECOG Performance Status (PS) to determine your ability to perform everyday activities (Standard of Care procedure)
- Vital signs – Blood pressure, pulse, temperature, and breathing rate measurements (Standard of care procedure)
- Blood tests (standard blood work);
- Biopsy of Pancreas - A fresh biopsy of your pancreas tumor may be necessary for researchers to archive for future analysis if archived tumor tissue is not available (research procedures)
- Urinalysis – (urine will be collected to check the function of your kidneys) standard of care procedure
- For women of child bearing potential only - about 1 teaspoon of blood will be collected for a pregnancy test (standard of care procedures)
- Tumor Imaging Scans (standard of care procedures)
  - CT-Scan or MRI of your chest, abdomen, pelvis
- Electrocardiogram (ECG) – to check the activity of your heart (Standard of care procedures)
- Research blood work for DNA analysis and correlative studies
- Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) for research purposes
- Completion of the PROMIS Quality of Life (QOL) assessment to determine how you feel about your physical, mental and social quality of life

The following exams, tests or procedures must be completed 14 days prior to registration:

- Blood will be drawn to check the function of your heart, liver and kidneys
- Urinalysis – (urine will be collected to check the function of your kidneys)
- Pregnancy test will be done for women of childbearing potential
- Check your height and weight

Study Treatment

Treatment Overview

If you decide to participate in this study you will take a low dose of only Nintedanib, twice daily for about the first 2 weeks. Once the researchers have determined that you can tolerate the low dose of Nintedanib, and have not experienced any study drug side effects that would stop you from continuing your treatment, you will receive the same low dose or a higher dose of Nintedanib along with gemcitabine plus nab-Paclitaxel as described in the table below:

Monotherapy Phase (2 weeks)	Combination Phase		
Nintedanib **150** mg twice daily, Days 1-14	Nintedanib **150** mg twice daily, Days 1-28	Gemcitabine 1000 mg/m^2, Days 1, 8, and 15	Nab-Paclitaxel 125mg/m^2 Days 1, 8, 15
Nintedanib **200** mg twice daily, Days 1-14	Nintedanib **200** mg twice daily, Days 1-28	Gemcitabine 1000 mg/m^2, Days 1, 8, and 15	Nab-Paclitaxel 125mg/m^2 Days 1, 8, 15

NOTE: Nintedanib will not be taken on the days that chemotherapy is infused – Days 1, 8 and 15 of the 28-day cycles.

You will be given a daily pill diary to complete as you are taking the study drug Nintedanib. Bring the completed form with you to every clinic visit to be reviewed by the researcher.

Monotherapy Phase: Treatment will start with Nintedanib monotherapy in a two week period (Days 1-14) before the combination phase is started, study MRIs will be obtained before the monotherapy phase and prior to the combination therapy phase. Archival tissue or a fresh biopsy will be obtained prior to starting treatment in the monotherapy phase.

Combination Therapy Phase: The combination phase will include gemcitabine + nab-paclitaxel, and Nintedanib. The treatment will consist of gemcitabine + nab-

Paclitaxel administered intravenously on days 1, 8, and 15 every 28 days. Nintedanib will be taken by mouth twice a day except on chemotherapy treatment days. You will stop Nintedanib the night before your chemotherapy and take Nintedanib on days 2, 9, and 16, if no treatment conditions exist that would prevent continued treatment with Nintedanib.

Treatment Assessments

Participation in this study will involve several procedures. Many of these procedures are part of the normal process of treating tumors such as yours. However, some of these procedures can be uncomfortable, inconvenient or painful. In addition to the procedures associated with the administration of Nintedanib and gemcitabine plus nab-paclitaxel as detailed above, you will be asked to participate in other procedures as part of your involvement in this study.

1. **Blood tests (including standard blood work and research blood work for DNA analysis and correlative studies):** Blood will be drawn from your vein or central line prior to the administration of Nintedanib and gemcitabine plus nab-paclitaxel up until the time you are no longer receiving Nintedanib. No more than 45 ml (3 tablespoons) of blood will be collected at any one time. Research draws will include draws for pharmacogenomics (DNA sample)_and pharmacodynamics (PD) samples for correlative studies.

2. **Tumor Imaging (CT or MRI) Scans:** Imaging test will be performed prior to enrollment in the study and every 8 weeks up until the time you are no longer receiving Nintedanib. These are standard of care procedures. A research-related DCE-MRI will also be performed at the end of the monotherapy phase.
3. **Physical Exam including Vital Signs:** At the beginning of each new treatment cycle (Day 1, of each cycle), a Physical Exam, performance status with vital signs will be performed;
4. **Side Effect and Medication Assessment:** Information on side effects of both treatments and new medications will be recorded. These are a research procedures to document drug toxicity assessment and drug compliance and accountability.
5. **PROMIS Quality of Life (QOL) assessment:** You will complete this questionnaire to determine how you feel about your physical, mental and social quality of life These are research procedures.
6. **Study Drug Diary:** You will be asked to complete a daily "diary" to note the date and time that you take your capsules of Nintedanib and to record any side effects that you may experience. These are research procedures.

Post-Treatment Follow-up (3-4 Hours)
After you have stopped taking Nintedanib, you will be asked to complete the following procedures:

1. **Blood tests:** Blood will be drawn from your vein or central line for safety evaluations post study drug;
2. **Urinalysis:** Urine will be collected to determine safety evaluation post study drug;
3. **Tumor Imaging (CT or MRI) Scans:** Imaging test will be performed to assess your tumor post study drug;
4. **Physical Exam including Vital Signs:** a Physical Exam, performance status with vital signs will be performed to assess your condition post study drug;
4. **Side Effect and Medication Assessment –** Information on side effects or both treatments and new medications will be recorded

Follow-Up Phase (10 min)
During the follow-up phase of this study, we will contact you via phone, review of your medical record, or certified mail to collect survivorship information.

How long can I expect to be in this study?
This study includes a treatment phase of up to 9 cycles and long-term follow-up for survivorship. Based on your response to treatment and at your doctor's clinical assessment and determination, you may continue to receive the study drugs after the 9 cycles. Clinical assessment will help your doctor to determine how many cycles of the drugs you are able to tolerate. You will have one follow-up visit within 7 days of stopping Nintedanib and an additional follow-up visit within 30 days of stopping Nintedanib for a safety evaluation. These visits will consist on standard blood test, imaging, and evaluation of any side effects that you may have experienced on the study.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Study Procedure/Intervention

Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider. If you receive active trial medication, then side effects may occur. Some of those side effects can be treated. Some side effects may go away when you stop taking the trial medication. Some side effects can be mild, but others may continue longer or become permanent. Some may be life-threatening or fatal.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or breathing difficulties. If you think you are having an allergic reaction, call the trial doctor right away. Patients who have known allergies to the study medications or its ingredients should not take part in this study.

In clinical trials, the most frequently reported side effects associated with the use of nintedanib include diarrhea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased. All identified side effects of nintedanib are listed below:

Gastrointestinal disorders
Diarrhea
Vomiting
Nausea
Abdominal pain
Pancreatitis

Hepatobiliary disorders
Drug-induced liver injury
Hepatic enzyme increased

- Alanine aminotransferase (ALT) increased
- Aspartate aminotransferase (AST) increased
- Blood alkaline phosphatase (ALKP) increased
- Gamma glutamyltransferase (GGT) increased

Hyperbilirubinemia

Vascular disorders
Hypertension
Bleeding (this term represents a group of events that describe a broader medical concept rather than a single condition or MedDRA preferred term; non-serious and serious bleeding events, some of which were fatal, have been observed in the post-marketing period)

Blood and lymphatic system disorders
Thrombocytopenia

Metabolism and nutrition disorders
Decreased appetite
Weight decreased

Skin and subcutaneous tissue disorders
Rash
Pruritus
Alopecia (hair loss)

Nervous system disorders
Headache

The risks of this study are primarily related to the combination chemotherapy (Nintedanib and gemcitabine plus nab-paclitaxel), and the biopsy of your pancreatic tumor. The risks listed below are based on a total of 1932 subjects who have been treated with Nintedanib.

Treatment with Nintedanib alone as single agent or in combination with standard doses of chemotherapy

Very common (equal or more than 10%):

- diarrhea (loose stools)
- nausea
- vomiting
- increased liver function tests (blood tests that show the liver is not working the way it should)
- decreased appetite
- low white blood cell count (which can make it easier to catch an infection)
- pain e.g., abdominal pain, chest pain, back pain, tumor pain, severe stomach pain
- skin problems such as: itching rash, hair loss, hand-foot syndrome, nail disorder
- abnormal skin sensations
- bleeding e.g. epistaxis (nose bleeds), coughing up small amounts of blood, rectal bleeding
- mouth ulceration
- weight loss
- weakness, numbness, and pain from nerve damage
- Fatigue
- Shortness of breath, inflammation of the nasal cavaties, inflammation of the lungs, cough and scarring of the lungs
- Alopecia (hair loss)

Common (equal or above 1% but below 10%):

- Taste changes
- Constipation
- Fever
- Anemia (low level of hemoglobin in your blood)

- High blood pressure
- Headache
- Infections (including those in the urine, chest, and sinuses)
- Dry mouth
- Flatulence (gas)
- Dizziness
- Dehydration
- Insomnia (difficulty sleeping)
- Chest pain
- Thromboembolism (obstruction of blood vessel by blood clot)
  Neutropenia - Low white blood cell count (which can make it easier to catch an infection)
- Hyperbilirubinemia - High levels of bilirubin in blood (which can cause yellowing of skin)
- low thyroid function
- respiratory infection
- pneumonia (infection of one or both of the lungs)
- Sepsis (body's response to an infection that releases chemicals to fight off infection).
- Abscesses (collection of pus that has built up within the tissue of the body)

Uncommon (less than 1%):

- Cough
- Chills
- Vertigo (loss of balance)
- Low blood pressure or high blood pressure
- Eye disorders, such as eye dryness, eye redness, conjunctivitis (pink eye), blurred vision
- Drug hypersensitivity (which can be a reaction or intolerance of the drug)
- Skin swelling
- Abnormal heart beats, fast or slow heart beats
- Low blood sugar
- Changes in kidney function
- Perforation (holes in the bowels)
- Bleeding into the brain
- Pancreatitis (swelling and inflammation of the pancreas)
- Constipation
- Depression
- Dry skin and hair
- Hoarseness or husky voice
- Muscle cramps and stiffness
- Tiredness or weakness
- Weight gain
- Low blood platelet count which increases the risk of bruising and bleeding

These treatment-related adverse events were usually reversible and most of these adverse events can be treated or resolved by temporarily or permanently stopping Nintedanib. If you experience any of these side effects or any other side effect which might be related to the intake of the study drug(s), your study doctor may adjust your

medication and give you advice on how you can minimize these side effects.

In a few patients a concurrent increase of bilirubin and liver enzymes was observed. This was fully reversible and appeared in the context of progression of the underlying cancer disease and concomitant development of liver metastases. Enzyme elevations generally normalized upon interruption of treatment in the majority of patients and did usually not recur after continuation of treatment at a reduced dose. The level of liver enzymes will be monitored closely during the conduct of this study. Extra blood sampling and imaging by e.g. ultrasound may be performed in order to clarify the potential underlying reason

for the increased liver enzyme values. If the cause for the altered liver function cannot be found, further investigations may be performed, this may include additional blood sampling for e.g. an extended analysis of safety parameters, the analysis of the types and amounts of hormones and the presence of viruses. Please tell your research doctor if you notice yellowing of the skin or of the white part of your eyes which are signs of an increase of the bilirubin-level in your body system.

Pre-clinical studies in animals indicate that impairment of immune function may also occur when being treated with Nintedanib. Such pre-clinical studies also indicated that Nintedanib in combination with natural sunlight or artificial UV radiation may cause effects to the skin or the eye. However, thus far, these adverse events have not been reported in clinical trials with humans.
You need to tell your trial doctor or a member of the trial team immediately if you experience any side effects.

***Nab-Paclitaxel* Risks**
In a previous study in patients with metastatic pancreatic cancer, an increase of blood infections was observed in patients who received the combination of *nab*®-paclitaxel and gemcitabine. You may not have the same risk of blood infections as metastatic pancreatic cancer patients; however, contact your study doctor immediately if you develop a fever. Your study doctor will evaluate if your fever is an early sign of a serious infection, for which antibiotics may be provided.

A particular lung illness, known as pneumonitis (inflammation of lung tissue), was observed in subjects (less than 1%) receiving *nab*®-paclitaxel alone or gemcitabine alone, but appears to occur more often (3%) when the two drugs are given together. This illness requires early detection and treatment as it may be life-threatening or even fatal. Therefore, it is important that you promptly tell your study doctor if you have worsening shortness of breath, difficulty breathing, fever, or a dry cough (not productive), for further evaluation and possible treatment.

The following is a list of the most common side effects reported in previous studies and considered to be related to *nab*®-paclitaxel. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy and some may never go away. The study doctor may alter the dosage regimen of *nab*®-paclitaxel or give you medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

Very common (a 10% or more chance that this will happen):

- Anemia (a decrease in the number of red blood cells which may make you feel weak or tired)
- Low number of white blood cells with or without fever (that may make it easier to get infections)
- A decrease in the number platelets, the cells that help your blood to clot (which may lead to unusual bleeding or bruising under the skin)
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Stomach pain
- Pain, swelling or sores on the inside of the mouth
- Dizziness
- Feeling tired or weak
- Pain (including muscle, joints, and chest pain)
- Swelling caused by fluid held in the tissues, especially of the ankles, feet or fingers
- Fever
- Chills
- Decreased appetite
- Change in taste
- Weight loss
- Difficulty sleeping
- Depression
- Neuropathy, a disorder of the nerves which can cause tingling or numbness, with weakness, or decreased sensation or movement
- Cough
- Shortness of breath
- Hair loss
- Rash, possible red, bumpy or generalized
- Itchiness
- Change in nails, including discoloration or separation from nailbed
- Abnormal liver functions test results
- Dehydration (loss of water and minerals in the body)
- Nose bleed
- Decreased potassium levels in blood

Common (between a 1% to less than 10% chance that this will happen):

- Bone marrow depression which is a severe reduction of red or white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely
- Watery eyes
- Change in vision or blurry vision
- Indigestion or upset stomach
- Trouble swallowing
- Abnormal chemistry or electrolyte blood test results
- Inflammation of the lung passages

- Thickening, inflammation or scarring in the lungs which may cause breathlessness, cough
- Inflammation of the bowel causing abdominal pain or diarrhea
- Infections, including pneumonia of the lung, mouth, gallbladder, urinary tract, nail, or hair follicle (which may be bacterial, fungal or viral)
- A very severe infection of the blood which may include a decrease in blood pressure
- Blockage of the intestine
- Trouble swallowing
- Indigestion or upset stomach
- Abnormal chemistry or electrolyte blood test results
- Acute kidney failure
- Blood in urine
- Lack of muscle coordination
- Muscle weakness
- Anxiety
- Nasal congestion
- Mouth and throat pain
- Dry mouth, nose, and throat
- Coughing up blood or bloody sputum
- Fluid in the chest cavity
- Blood clot in the lungs or deep vein
- Changes in nails, including discoloration
- Red or flushed skin
- Dry skin
- Hand-foot syndrome, involving reddening, swelling, numbness and peeling of palms and soles of feet
- High blood pressure
- Low blood pressure
- Faster heartbeat
  Headache
- A decrease in the heart's ability to pump blood to all parts of the body and possibly heart failure
- Infusion site reactions (described as discomfort, bleeding or bruising/swelling at the needle site, and in some instances infection or leaking of IV fluid outside of the blood vessel into the surrounding tissue.
- Localized swelling due to build-up of lymph fluid

<u>Uncommon (between a 0.1% to less than 1% chance that this will happen):</u>

- Irregular or slow heart beat
- A decrease in the left side of the heart's ability to pump blood to all parts of the body and possibly heart failure
- Stopping of the heart
- Syndrome involving abnormal blood clotting, with decreased platelets, bruising (including tiny red or purple spots under the skin), and possible leading to blood clots.
- Irritation and redness of the thin membrane covering the eye
- Inflammation of the cornea
- Feeling unwell

- Sleepiness
- Allergic reaction (may include skin inflammation, rash, trouble breathing; trouble speaking; fever, and/or diarrhea); sometimes fatal
- Too much fluid in the body
- Scaly or peeling skin
- Hives

Additional side effects that have been reported by patients who have taken *nab*-paclitaxel outside of a study, not otherwise noted above include:

- Edema/swelling and cyst formation of the macular area of the retina
- A loss of nerve function in the muscles of the face
- Lack of movement in the vocal cords with possible voice changes
- Skin sensitivity to sunlight
- Potentially life threatening condition of the skin and oral mucous membranes (may include lesions in the mouth, itching and blistering skin)
- Skin or tissue damage from prior radiation therapy can become damaged again, when a person receives chemotherapy after having had radiation therapy. This is referred to as radiation recall and may involve redness, peeling, pain, and swelling. Skin changes have been noted to range from mild redness to tissue death. Radiation recall may also occur in the lungs and other internal organs

Gemcitabine Risks

The most common side effects of gemcitabine include:

- Low platelet count (which can lead to bruising or bleeding)
- Low red blood cell count
- Infections due to low white cell blood count
- Abnormal liver function
- Blood and protein in the urine
- Nausea and vomiting
- Diarrhea (loose stools)
- Constipation (difficult bowel movement)
- Mouth and lip sores
- Fluid retention (swelling of the hands, feet or face)
- Fever
- Rash
- Difficulty breathing
- Flu-like symptoms (fever, feeling tired, loss of appetite, chills and cough)
- Hair loss
- Tingling, prickling of the skin
- Itching

The least common side effects of gemcitabine include:

- Irritation and bruising at site of infusion
- Allergic reaction
- Failure of your kidneys
- Severe difficulty breathing
- Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may

cause headache, seizure, blindness

You should inform your study doctor if you are planning any invasive medical procedures while receiving treatment with gemcitabine, as some subjects have an increased risk of bleeding.

Risk of Pancreatic Tumor Biopsy:

Occasional (Less than 20% of patients):

- Pain at site of biopsy

Rare but serious (Less than 2% of patients):

- Bleeding from pancreas
- Difficulty breathing
- Death

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control while participating in this study and for 3 months after your last dose of the study drug. Medically-acceptable forms of birth control include:

(1) Surgical sterilization (vasectomy); or

(2) A condom used with a spermicide (a substance that kills sperm).

Females: As with any investigational drug, the effect of Nintedanib on an unborn child is unknown. If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study.

You must be willing to have a pregnancy test done before beginning your participation, regularly at trial visits, and at the end of the trial and beyond for at least 3 months after the last dose of Nintedanib (for Nintedanib monotherapy), or up to 3 months (for combination therapy: duration is defined by the compound with the longest contraception duration according to the respective label) after end of active treatment. If you take part in this study and you are sexually active, you and any person that you have sex with must use medically-acceptable birth control (contraceptives) during the study and for 3 months after your last dose of the study drug.

Medically-acceptable birth control (contraceptives) includes:

(1) Surgical sterilization (such as hysterectomy or “tubes tied”);

(2) Approved hormonal contraceptives (such as birth control pills, patch or ring;

Depo-Provera, Depo-Lupron, Implanon);
(3) Barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm); or
(4) An intrauterine device (IUD).

Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant. When there is complete sexual abstinence, the patient refrains from any sort of sexual activity that could involve the spill of an ejaculate, even if the spill does not occur.

If you are pregnant or think you could be pregnant, it is important for you to tell the trial doctor or trial staff immediately. If you become pregnant during the trial, you will be removed from the trial and your health and your baby's health will be monitored throughout your pregnancy. Even if you are no longer in the trial, your trial doctor will contact you after your baby is born to find out about the baby's health.

Risks of Radiation-Diagnostic Test
The radiation dose that you will get from diagnostic tests is medically indicated for your condition and it is the same that you would get if you were not involved in this research study.

CT-Scan
Computed tomography (CT) scans use X-ray radiation. Some CT scans require you to take a "contrast solution". It is possible that the contrast solution may cause you to have nausea, vomiting, itching, or skin rash. In rare cases, it may cause your throat to swell and make it hard to breathe. These may be signs of an allergic reaction so tell the study doctor right away if you have any of these side effects. You may have some discomfort from lying still in an enclosed space for a prolonged period of time.

MRI
An MRI does not use x-ray radiation, but it takes a little longer and participants sometimes have to lie in a more enclosed space. A contrast agent may be injected into your vein before the scan is done to help the doctor see the tumor more clearly. There are no known risks from exposure to magnetic fields. You may experience nervousness and/or anxiety due to the loud banging made by the machine while it is taking pictures and from confinement in a tight space (claustrophobia). If you become anxious, you can stop the procedure at any time.

You may also experience some discomfort and fatigue from lying still during imaging.

If you have any metal clips or plates in your body, you should tell the investigator. MRI may not be appropriate if you are pregnant or are trying to become pregnant. MRI may not be appropriate if you have permanent eyeliner or eyebrows or any pieces of metal in your body, such as the following:

• heart pacemaker, heart valve replacement, or aortic clips
• metal fragments in your eyes, skin, or elsewhere in your body
• brain clips or pieces of metal used in aneurysm surgery or intercranial bypass
• venous umbrella

• pieces of metal in the body resulting from work as a sheet-metal worker or welder
• clips placed in an internal organ
• prosthetic devices, such as middle ear, eye, joint, or penile implants
• joint replacement.
• hearing aid that cannot be removed
• neurostimulator
• insulin pump
• intrauterine device (IUD)
• shunts or stents
• metal mesh or coil implants
• metal plate, pin, screws, or wires, or any other metal implants

If you have a history of an implanted device or clips in your pelvis (involving your uterus or fallopian tubes) or under your skin, acting as a contraceptive to prevent pregnancy, the MRI technologist will obtain specific information about the make and model of your implanted device to determine if it is safe for you to receive the MRI examination.

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called Gadolinium (dye solution used to highlight organs or tissues during imaging). The injection of Gadolinium may cause discomfort like headache, nausea, strange taste, or coldness at site of injection. These symptoms occur in less than 1 out of 20 patients receiving Gadolinium and go away quickly. There is a small

risk of a severe allergic reaction that can cause breathing difficulties and/or low blood pressure, and these symptoms are extremely rare (approximately 1 in 10,000 to 1 in 100,000 administrations). In the unlikely event you experience these symptoms, a physician and nursing staff will be available to evaluate and, if necessary, provide treatment.

People with severe kidney failure who receive Gadolinium (dye solution used to highlight organs or tissues during imaging) are at risk of developing a disorder called Nephrogenic Systemic Fibrosis (NSF). This disease can cause wide spread tissue scarring or hardening (fibrosis). In rare cases NSF can lead to lung and heart problems and cause death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF is 1-5%. We may perform a blood test 30 days before your MRI to check how well your kidneys are working before you receive the Gadolinium. This test may be repeated closer to your MRI appointment if your medical condition has changed. If your kidneys are working at levels known to be at risk for NSF, you will not receive Gadolinium. You will not receive Gadolinium for research purposes if you have sickle cell disease (a disease of the blood cells) since it may put you at risk of developing hemolysis (breakdown of blood cells).

<u>Risks of Blood Drawing</u>
Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

You will have approximately 39 tablespoons of blood collected because you are in this

research study. The amount collected may vary depending on how long you are able to participate.

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?

Study risks will be minimized or prevented by several measures at the beginning of the study and throughout your participation in the study. You will be screened prior to enrollment to assure that you meet the safety requirements of the study. All treatments will be modified within the study parameters to match your treatment needs. These modifications will include the area being treated with chemotherapy. Throughout your participation in the study you will be evaluated by personnel trained to recognize, minimize, and treat side effects of your treatment. You will be withdrawn from the study if you experience an adverse event which causes unacceptable risk as determined by the research doctors. You will continue to receive standard medical care if you are no longer participating in the study.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand;
- Keep your appointments;
- Follow the researchers' instructions;
- Let the researchers know if your telephone number or address changes.
- Store study materials and capsules in a secure place at home away from anyone who is unable to read and understand labels, especially children;
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter;
- Tell your regular doctor about your participation in this study;
- Report to the researchers any injury or an illness while you are on study, even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?

If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?
If you agree to take part in this study, there may or may not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others with advanced pancreatic cancer in the future. Information gained from this research could lead to better care and treatment.

What options are available if I decide not to take part in this research study?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- To receive standard of care treatment as advised by their physician.
- To not receive any care.
- To participate in another clinical trial.

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?
No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Will my insurance provider or I be charged for the costs of any part of this research study?
Yes, Most of the procedures during this study are considered standard of care and will be billed to you and/or your insurance provider.

However, procedures during this study that are preformed specifically for the research study (e.g.: second biopsy (optional), research blood (biomarkers and DNA), and study drug (Nintedanib) will be paid for by the sponsor of the study.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center or Boehringer Ingelheim.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?
Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Simmons Comprehensive Cancer Center Phase 1 Disease Oriented Team
- Simmons Comprehensive Cancer Center Data Safety and Monitoring Committee
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board;
- Boehringer Ingelheim, the drug suppler and its authorized agents;
- Governmental agencies in other countries where the study drug may be considered for approval.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by the 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.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information". This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Whom do I call if I have questions or problems?
For questions about the study, contact Salwan Al Mutar, MD at: 214-648-4008; during regular business hours and at 214-645-4673, after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

_____

Name of Participant (Printed)

_____ _____ _____ AM / PM

Signature of Participant Date Time

_____

Legally Authorized Representative's Name (Printed)

_____ _____ _____ AM / PM

Legally Authorized Representative's Signature Date Time

_____

Name of Person Obtaining Consent (Printed)

_____ _____ _____ AM / PM

Signature of Person Obtaining Consent Date Time