

**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY**

**CC#144515: Perioperative Stromal Depletion Strategies in Pancreatic Ductal
Adenocarcinoma**

This is a clinical trial, a type of research study. Your study doctor(s), Andrew Ko, M.D or Margaret Tempero, M.D., or one of their associates from the University California San Francisco Gastrointestinal Oncology Division will explain the clinical trial to you

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have pancreatic cancer that, at this time, may be removed by surgery. The study will determine if the drugs being used will increase the likelihood that your tumor will be removed successfully by surgery in the future.

Why is this study being done?

Pancreatic cancer is a difficult cancer to treat because we do not have many treatment options. Although it is routine practice to treat pancreatic cancer with chemotherapy, pancreatic tumors are less sensitive to chemotherapy than other kinds of cancer. One reason that chemotherapy is less effective for pancreatic cancer may be that the drugs cannot reach the tumor cells because they are surrounded by a barrier of thick fibrous (scar-like) tissue. This fibrous tissue is thought to prevent flow of the chemotherapy drugs to the tumor cells by compressing the blood vessels which would otherwise deliver the drugs directly to the tumor.

A new drug, **PEGPH20**, was developed to treat pancreatic cancer in combination with other drugs. PEGPH20 is a protein enzyme which breaks down hyaluronan, an important component of the fibrous tissue surrounding pancreatic tumor cells. Early studies in animals with tumors showed that treatment with PEGPH20 broke down the fibrous tissue, allowing the blood vessels to open so that chemotherapy drugs can reach the tumor more effectively. In this study, participants will receive PEGPH20 in addition to chemotherapy.

Recent studies have shown improved survival in patients with pancreatic cancer that had spread to other organs who were given two chemotherapy drugs called nab-paclitaxel and gemcitabine. In this study, PEGPH20 is being combined with nab-paclitaxel and gemcitabine to find out if PEGPH20 can allow these chemotherapy drugs to work better, by improving the flow of blood and drugs to the tumor.

The purpose of this study is to find out if using PEGPH20 together with gemcitabine and nab-paclitaxel is safe and to monitor if patients experience any side effects. In addition, we will evaluate if this combination causes your tumor to shrink enough, so that it can be removed surgically.

Although we hope that PEGPH20 will breakdown the fibrous tissue so that chemotherapy can reach the tumor better, it is possible that doing so may also increase the risk of pancreatic fistula after your surgery. This is explained further in the risks section on page 15.

Gemcitabine and nab-paclitaxel have been approved by the FDA in the treatment of some types of pancreatic cancer. PEGPH20 has not been approved by the FDA for the treatment of pancreatic cancer.

This study will be conducted in 2 parts.

- In part 1, the first 15 participants will receive PEGPH20 for one week before starting chemotherapy with gemcitabine and nab-paclitaxel. This is called the ‘run-in period.’ If you are in part 1, you will also be asked to have 2 additional MRIs and 2 biopsies of your tumor- one MRI and biopsy before receiving PEGPH20 and one MRI and biopsy after receiving PEGPH20. The MRIs and biopsies will be done to find out if PEGPH20 is having an effect on your tumor.
- If treatment with PEGPH20 is determined to be safe and effective in the first 15 participants, an additional 21 participants will be enrolled in part 2. Participants enrolled in Part 2 of the study will not have the additional MRIs and biopsies mentioned above.

The study drug, PEGPH20, and gemcitabine and nab-paclitaxel will be given in clinic by intravenous (IV) infusion. This usually takes about 2-3 hours.

This study is being funded by the National Cancer Institute and Halozyme Therapeutics.

How many people will take part in this study?

Approximately 36 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the main part of the study:

Screening Period

If you choose to participate in this study, you will need to have the following tests and procedures to find out if you can be in the main part of the study (this is called ‘Screening’). Some of these tests and procedures are part of regular cancer care. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. There may be reasons you are not allowed to take part in this study. The study doctor or staff will discuss these with you.

The Screening Visit will take about 5-6 hours.

- You will have a complete physical exam and your current symptoms will be reviewed.

- You will be asked about your medical history including any past treatments or surgeries for your disease.
- Your vital signs, including height, weight, temperature, breathing rate, blood pressure, pulse, and oxygen in your blood levels will be recorded.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked about any side effects that you may be experiencing and how you are feeling.
- You will be asked about how easy or hard it is for you to carry out your daily activities.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein. The blood sample will be used for routine safety tests, and to test for Hepatitis B and a tumor marker called CA 19-9.
- If you are a woman of child bearing potential, you will have a blood or urine pregnancy test.
- You will have a **CT** or **MRI** scan of your chest, stomach, and pelvis. The type of scan will be determined by the study doctor.
 - A **CT** scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about 30 minutes.
 - An **MRI** scan takes an image of your body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed, which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the Radiology Department and takes approximately an hour and a half to complete.

Additional Screening for Participants in Part 1 only

If you are participating in Part 1 of the study, the following tests and procedures will be done in addition to those listed above before receiving PEGPH20. If you are participating in Part 2 of the study, you will not have the following tests and procedures done:

- You will have a functional MRI (fMRI) scan. An fMRI is a special type of MRI that can show changes in blood flow. The process for having an fMRI scan done is the same as having an MRI done (described above). An fMRI will also be performed after the 1 week run-in with PEGPH20 alone to see if blood flow to the tumor improved after receiving PEGPH20.
- A biopsy of your tumor will be taken during a procedure called an endoscopic ultrasound. This biopsy sample will be tested and compared with a biopsy sample collected after the 1 week run-in with PEGPH20, to see if features of the tumor changed after taking PEGPH20. An endoscope is a thin, flexible tube with a small video camera and light on the end, so it can provide a clear and detailed view of the digestive tract. Ultrasound is an imaging method that uses sound waves to produce pictures. During an endoscopic ultrasound, a doctor uses an endoscope with an ultrasound processor at the end is used to examine the lining of the digestive tract, and surrounding structures like the pancreas. The doctor will insert a needle into the tumor and remove small pieces. The sample will be compared to the sample taken after you complete 1 week of PEGPH20, to see if the study drug has any effects on your cancer. For comfort purposes, you will receive a medication that will sedate you prior to procedure.

During the main part of the study:

If the exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, then:

- Participants in Part 1 will receive PEGPH20 alone for 1 week. Afterwards, participants in Part 1 will be given PEGPH20 with nab-paclitaxel and gemcitabine.
- Participants in Part 2 will receive PEGPH20 with nab-paclitaxel and gemcitabine (no 1-week run-in with PEGPH20 alone)

Participants in Part 1 only: 1 week run-in period with PEGPH20

The first 15 study participants will be in Part 1 of the study, which includes an additional 1 week ‘run-in period’ of receiving PEGPH20 alone (without nab-paclitaxel and gemcitabine).

- PEGPH20 will be given on Day 1 and Day 4 of the run-in period.
 - You will be asked to take **dexamethasone** by mouth 1-2 hours before you receive PEGPH20 and 8-12 hours after completion of PEGPH20. Dexamethasone is a steroid that is often given with chemotherapy drugs to reduce some side effects caused by chemotherapy. Also, it may help minimize or prevent muscle and/or joint pain that may be caused by PEGPH20.
 - Additionally, on the day that you start PEGPH20 you will begin taking a blood thinner medication called **enoxaparin**. This is to reduce the risk of blood clots while receiving PEGPH20. Before starting PEGPH20, nurses will teach you how to give yourself the injections. Enoxaparin is administered by injection under the skin using a small needle and syringe. You will self-inject this medication once a day. The medication comes in pre-filled syringes. You will identify an area on the side of your

stomach, at least 2 inches from your belly button. You will then clean the injection site with an alcohol swab. You can hold the syringe like a pencil in your writing hand and pinch an inch to make a fold in your skin with your other hand. You will insert the needle at a 90-degree angle into the fold of skin. You will then pull the needle from the skin fold and dispose the syringe.

You will be on enoxaparin as long as you are receiving PEGPH20 and for at least 14 days after your last infusion with PEGPH20. The study doctor and staff will let you know when to stop and re-start enoxaparin before and after procedures that might increase the risk of bleeding, such as biopsies or minor surgeries.

Note: it is not yet known whether enoxaparin is effective in reducing the risk of blood clots in patients who receive PEGPH20.

- A total of 1 tablespoon of blood will be taken by inserting a needle into a vein. The blood sample will be used to test for hyaluronan (HA), a substance in your blood related to tissue repair.
- You will be asked about any side effects that you may be experiencing and how you are feeling.
- On Day 8 of the run-in period, the following tests and procedures will be done:
 - You will have a functional MRI (fMRI) scan. An fMRI is a special type of MRI that can be used. The fMRI will be compared to the fMRI done before you started the 1 week run-in to see if blood flow to the tumor improved after receiving PEGPH20.
 - You will have a CT or MRI scan of your chest, stomach, and pelvis.
 - A biopsy of your tumor will be taken during a procedure called an endoscopic ultrasound (this is the same type of biopsy that was done before you started PEGPH20). This biopsy sample will be tested and compared with the biopsy sample collected before you started PEGPH20, to see if features of the tumor changed after taking PEGPH20.

After you complete the run-in period with PEGPH20 alone, you will begin receiving PEGPH with nab-paclitaxel and gemcitabine within 1-2 weeks.

All Participants: PEGPH with nab-paclitaxel and gemcitabine

During the main part of the study, all participants will receive 4 cycles of PEGPH with nab-paclitaxel and gemcitabine. Each cycle is 28 days (4 weeks).

PEGPH20, nab-paclitaxel and gemcitabine will be given through a vein on days 1, 8, and 15 of each cycle (you will receive study drugs weekly for 3 weeks, followed by 1 week off, for each 4-week cycle).

PEGPH20 will be given through a vein for about 10 minutes. Approximately 2-4 hours afterwards, you will receive nab-paclitaxel for 30 minutes. Then you will be given gemcitabine for about 30 minutes.

- You will be asked to take **dexamethasone** by mouth 1-2 hours before you receive PEGPH20 and 8-12 hours after completion of PEGPH20. Dexamethasone is a steroid that is often given with chemotherapy drugs to reduce some side effects caused by chemotherapy. Also, it may help minimize or prevent muscle and/or joint pain that may be caused by PEGPH20.
- Additionally, on the day that you start PEGPH20 you will begin taking a blood thinner medication called **enoxaparin**. This is to reduce the risk of blood clots while receiving PEGPH20. Before starting PEGPH20, nurses will teach you how to give yourself the injections. Enoxaparin is administered by injection under the skin using a small needle and syringe. You will self-inject this medication once a day. The medication comes in pre-filled syringes. You will identify an area on the side of your stomach, at least 2 inches from your belly button. You will then clean the injection site with an alcohol swab. You can hold the syringe like a pencil in your writing hand and pinch an inch to make a fold in your skin with your other hand. You will insert the needle at a 90-degree angle into the fold of skin. You will then pull the needle from the skin fold and dispose the syringe.

You will be on enoxaparin as long as you are receiving PEGPH20 and for at least 14 days after your last infusion with PEGPH20. The doctor and staff will let you know when to stop and re-start enoxaparin before and after procedures that might increase the risk of bleeding, such as biopsies or minor surgeries.

Note: it is not yet known whether enoxaparin is effective in reducing the risk of blood clots in patients who receive PEGPH20.

During the main part of the study, the following tests and procedures will be done:

Days 1, 8, 15 of each cycle (Every time you receive study drugs):

- Your weight and vital signs, temperature, breathing rate, blood pressure, pulse, and oxygen in your blood levels will be recorded.
- You will be asked about any side effects that you may be experiencing and how you are feeling.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein. The blood sample will be used for routine safety tests and to test for Hyaluronan (HA).
- You will be asked about any side effects that you may be experiencing and how you are feeling.

Day 1 of each cycle (every 4 weeks):

- You will have a complete physical exam and your current symptoms will be reviewed.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked about how easy or hard it is for you to carry out your daily activities.
- Your blood will be tested for a tumor marker called CA 19-9. No additional blood will be drawn for this test, we will use the blood drawn for safety testing.

Every 8 weeks:

- You will have a CT or MRI scan of the chest, stomach, and pelvis.
 - If you are participating in Part 1 of the study (if you received 1 week of PEGPH20 alone), and imaging done after you finish receiving study drugs shows that you are eligible for surgery, you will be asked to have an additional fMRI scan. The fMRI scan will be done to look for changes in the tissue surrounding the pancreatic tumor.

End of Treatment Visit:

- You will have a complete physical exam and your current symptoms will be reviewed.
- Your weight will be recorded.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked about any side effects that you may be experiencing and how you are feeling.
- You will be asked about how easy or hard it is for you to carry out your daily activities.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein. The blood sample will be used for routine safety tests, and to test for a tumor marker called CA 19-9.
- If you had surgery, the study doctor may talk to you about getting 2 cycles of chemotherapy, without PEGPH20, after you have recovered from surgery.

How long will I be in the study?

You will be given PEGPH20, nab-paclitaxel and gemcitabine, as long as your cancer is not getting worse and you do not experience bad side effects, for about 4 months. We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone every 2-3 months to see how you are doing. Keeping in touch with you and checking on your condition helps us look at the long-term effects of the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the PEGPH20, nab-paclitaxel and gemcitabine can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the PEGPH20, nab-paclitaxel and gemcitabine. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Risks of PEGPH20

Possible side effects that may be related to PEGPH20 are listed below. These lists are based on reported side effects from approximately 272 patients who have received PEGPH20 in previous cancer studies (including studies in pancreatic cancer). In these studies PEGPH20 was either used alone or in combination with chemotherapy.

Very common side effects (observed in more than 10% of people)

- Musculoskeletal effects (such as muscle cramps, muscle spasms). Dexamethasone or other anti-inflammatory medicines have been given with PEGPH20 in previous studies to decrease the severity of these musculoskeletal side effects.
- Nausea
- Diarrhea
- Vomiting
- Swelling in arms/legs due to fluid accumulation
- Fatigue (feeling tired)
- Joint pain
- Abdominal pain
- Abnormal platelets which help with clotting
- High liver enzyme level
- Distortion to the sense of taste
- Decreased appetite

Common side effects (observed in between 1% to 10% of people)

- abdominal pain
- constipation
- gastro esophageal reflux [a build-up of stomach acid which may move into the esophagus (the tube that carries food from your mouth to your stomach)]
- flu-like symptoms (such as headache, chills, dizziness, muscle weakness, stiffness or pain, flushed skin)
- dry skin
- itching or rash
- hair loss

- abnormal heart rates or rhythms
- difficulty breathing
- pneumonitis (inflammation of swelling of lung tissue)
- nose bleeds
- blood clots
- high or low blood pressure
- dehydration (loss of body water)
- high blood sugar
- feelings of numbness in your hands and/or feet
-
- urinary tract infection
- cerebrovascular accident (stroke)
- muscle weakness
- arm or leg pain
- musculoskeletal pain
- back pain
- bone pain
- joint stiffness
- chest discomfort
- abdominal bloating
- face swelling
- dry mouth
- difficulty swallowing
- low albumin levels
- low sodium levels
- low potassium levels
- high magnesium levels
- dizziness
- headache
- difficulty balancing
- dysphonia (difficulty speaking)
- sore throat
- hiccups
- fluid in lung tissue
- cough
- hypoxia (oxygen shortage)
- decreased liver enzymes
- decreased white blood cell count
- weight loss
- yeast infection
- oral fungal infection
- cellulitis (skin infection)
- flushed skin
- insomnia

- confusional state
- blood in urine

Uncommon side effects (observed in 1% or fewer people)

- esophageal spasms (contractions of the tube that carries food from your mouth to the stomach)
- joint swelling or stiffness
- muscle tissue inflammation
- ECG abnormalities
- shortness of breath
- nasal congestion
- reduced sense of touch
- skin blisters
- orthostatic hypotension (or low blood pressure possibly experienced as dizziness that happens when you stand up from sitting or lying down positions)
- dry eye
- reduced vision or visual floaters (specks or strings floating in your vision)
- joint lock (reduced movement of joints)
- muscle tightness
- neck pain
- chest discomfort
- feeling hot
- weakness
- inflammation
- infections of the mucous membrane in the mouth
- gait disturbance
- stomach pain
- ascites (abdominal swelling)
- fecal incontinence (loose bowels)
- flatulence (gas)
- pain in mouth
- electrolyte imbalance (increase potassium, decreased calcium)
- restless legs syndrome
- hemiparesis (weakness of one side of the body)
- irregular breathing
- blood clot in lung
- increased kidney enzymes
- abnormal breath sounds
- low red blood cell count
- weight gain
- skin peeling
- increased sweating
- skin pain
- enlarged spleen

- pneumonia
- bronchitis
- upper respiratory infection
- cardiac disorders
- eye swelling
- bruises
- falling
- sleep disorders
- painful urination, urinary hesitation, urinary incontinence (inability to hold urine)
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- ear discomfort
- tinnitus (ringing in ears)
- amenorrhea (lack of menstrual periods)
- increased size of prostate
- decreased thyroid function
- hypersensitivity (allergic reactions)

Infusion reactions

Infusion reactions to PEGPH20 are not common, but possible. You may not participate in this research study if you are allergic to hyaluronidases (a component of PEGPH20). Symptoms of infusion reactions may include shortness of breath, rapid breathing, chest pressure and pain, ringing in the ears, wheezing, blurry vision, skin and/or facial redness, decrease in blood pressure and back pain.

Risks for blood clots

PEGPH20 may increase the risk of blood clots as noted in the section above. The exact reason why PEGPH20 may increase the risk is not known. Although a blood thinner is not routinely used to prevent blood clots in patients with pancreatic cancer, you will be given a blood thinner (enoxaparin) to help prevent blood clots during the study. It is currently unknown if enoxaparin will prevent blood clots; other patients have developed blood clots while taking enoxaparin. You should always report changes in your health to your study doctor. Symptoms of a blood clot may include pain in your legs or shortness of breath. If you experience either of these side effects, contact your doctor immediately for further treatment. If you have any questions regarding this risk, please discuss this with your study doctor, including ways to prevent the occurrence of blood clots (e.g., drinking plenty of fluids, compression stockings, and walking/moving your legs frequently). Your study doctor will continue to monitor you (per standard practice) for blood clots.

PEGPH20 with modified FOLFIRINOX

In a study that was not sponsored by Halozyme (the manufacturer of PEGPH20), PEGPH20 was given in combination with a type of chemotherapy called ‘modified FOLFIRINOX’. Participants in this study had metastatic pancreatic cancer and were not enrolled based on expression of the tumor marker hyaluronan (the sugar molecule that PEGPH20 targets). The results of this study showed that adding PEGPH20 to modified FOLFIRINOX increased bad side effects, such as diarrhea, vomiting, nausea, and fatigue, and reduced overall survival in these participants.

Risks of GEMCITABINE

The following severe side effects have been observed with gemcitabine (regardless of rate of occurrence):

- Gemcitabine may affect the blood cells in your bone marrow and result in decreased number of the red, white, and/or platelet blood cells.
- Gemcitabine may also affect your respiratory system and result in lung inflammation, scarred lungs, fluid in the lungs and lack of oxygen entering the lungs and/or lung failure.
- Gemcitabine may also affect the kidneys and possibly cause kidney failure.
- Hemolytic-uremic syndrome (which is a disorder occurring after a gastrointestinal infection) which may lead to any of the following complications: Blood in stool, irritability, fever, lethargy, vomiting/diarrhea, weakness, bruising, decreased consciousness, low urine output, no urine output, pale looking, seizure, skin rash that looks like fine red spots, and yellow skin.
- Gemcitabine may also affect your liver and cause liver enzyme increases; in addition, liver failure has been observed.
- Capillary Leak Syndrome (a rare, but serious, condition which causes generalized swelling and a rapid decrease in blood pressure)
- Posterior Reversible Encephalopathy Syndrome (a syndrome characterized by headache, nausea/vomiting, confusion, seizures and visual loss/disturbances)
- Severe allergic reactions (such as rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue)

The following side effects have been observed commonly with the use of gemcitabine:

- Decreased red and white blood cells and platelets
- increased liver enzymes
- protein in the urine
- blood in the urine
- decreased kidney function
-
-
-
-
- difficulty breathing
- diarrhea
- bleeding
- infection
- hair loss
- swelling of the hands/feet
- flu-like symptoms (consisting of fever, weakness, lack of appetite, headache, cough, chills
- muscle pain, trouble falling asleep, inflammation inside the nose, sweating, and/or weakness)
- neuro motor complications
- tingling, numbness

Risks of NAB-PACLITAXEL

The following severe side effects have been observed with the use of nab-paclitaxel (regardless of rate of occurrence):

- Nab-paclitaxel may affect the blood cells in your bone marrow and result in decrease of the red, white (including neutrophils, a type of white blood cells important in fighting against bacterial infections), and/or platelet blood cells (important for clotting and to control bleeding).
- Sepsis (a severe blood infection)
- Pneumonitis (inflammation or swelling of lung tissue)
- Nab-paclitaxel may affect the neurologic system and may cause numbness, tingling, or burning in your hands or feet (neuropathy).
- Severe sometimes fatal hypersensitivity reactions have occurred with nab paclitaxel. This includes Stevens-Johnson syndrome (a skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth).

The following side effects have been observed commonly with the use of nab-paclitaxel:

- Hair loss
- numbness or tingling in the hands or feet

- abnormal heart beat
- tiredness
- joint and muscle pain
- changes in your liver function
- low red blood cell count. (tell your doctor if you feel weak, tired or short of breath)
- nausea
- infections (tell your doctor right away if you have a fever greater than 100.4oF or other signs of infection)
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Risks of PEGPH20 in combination with NAB-PACLITAXEL and GEMCITABINE

In a recent clinical study in 111 pancreatic cancer patients who received PEGPH20 in combination with nab-paclitaxel and gemcitabine the following side effects were seen:

Very common (observed in 10% or more people):

- muscle spasms (repeatedly spontaneous contractions of your muscles)
- muscle pain
- muscle weakness
- joint pain
- blood clot in lung
- fatigue
- swelling in the legs
- nausea
- diarrhea
- abnormal platelets which help with clotting
- high liver enzyme level
- a distortion to the sense of taste

Common (observed in 1% to 10% of people):

- infusion-related reaction
- Clotting of blood in vessels in different parts of the body: (such as brain, arms/legs, lungs, bowel system)
- pain in one of your extremities
- back pain
- bone pain
- joint stiffness
- joint swelling
- musculoskeletal pain

Uncommon (observed in less than 1% of people):

- musculoskeletal stiffness
- muscle inflammation
- neck pain

The following side effects were more common in patients treated with PEGPH20 plus nab-paclitaxel and gemcitabine compared to nab-paclitaxel and gemcitabine without PEGPH20:

- Swelling in the legs
- muscle spasms
- muscle pain
- lower platelets.

Risks of ENOXAPARIN

Common side effects include:

- nausea
- diarrhea
- swelling in your hands or feet
- mild swelling, pain, bruising, or redness where the medicine was injected

More serious side effects may also include:

- hives (swollen, pale red bumps on the skin that appear suddenly)
- itching or burning skin
- difficulty breathing
- purple or red pinpoints under skin
- feeling light-headed or short of breath
- rapid heart rate
- black or bloody stools
- coughing up blood or vomit that looks like coffee grounds
- swelling of your face, lips, tongue, or throat
- numbness; tingling or muscle weakness (especially in your legs and feet)
- severe headache
- problems with speech, vision, or balance

If you experience any of these serious side effects, stop using enoxaparin and call the study doctor right away.

Additional Risks

- **Biopsies obtained at the time of endoscopy:** The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure can be unsuccessful and require a repeat

biopsy to get enough tissue. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

- **CT scan risks:** CT scans involve the risks of radiation. In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan wif you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects.
- Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected by vein. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.
- **Radiation Risk:** This research study involves exposure to radiation. All this radiation exposure is necessary for your medical care and is not for research purposes. This amount of radiation may involve a low risk of cancer. However, we believe that this risk, given your overall medical condition is not clinically relevant. If you are pregnant or breast feeding, you SHOULD NOT participate in this study. If you have any questions regarding the use of radiation or the risks involved, please consult your study doctor.
- **MRI risks:** Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than on in one thousand), patients are allergic to gadolinium. These

effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.
- **Surgery:** Surgery may be associated with pain, bleeding, infection, difficulty with wound healing and digestion.
- **Pancreatic fistula:** A fistula is an abnormal connection between an organ, vessel, or intestine and another structure and is usually the result of injury or surgery. It can also result from infection or inflammation. Formation of a pancreatic fistula is a common complication of surgery to remove pancreatic tumors, and occurs when the main pancreatic ducts or tissues that produce tissue digesting enzymes are injured. This damage causes the pancreatic enzymes to leak through drain sites or wounds, and into surrounding areas of the pancreas to create more tissue damage. Although PEGPH20 has not been tested in patients who will undergo surgery to remove their tumors, there is the possibility that using PEGPH20 to change the tissues around your tumor may increase your risk of developing pancreatic fistula after surgery. In this study you will be closely monitored for any increase in risk of developing pancreatic fistula.
- **Study drug combination:** The side effects of the combination of PEGPH20, gemcitabine and nab-paclitaxel are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects.
- **Infusion:** As with most intravenous products, you may experience pain, irritation, swelling or bruising, or a slight chance of infection at the site where the intravenous catheter (small tube) is inserted into your vein. These side effects may also be observed at the site where blood is drawn for laboratory tests.

- **Intravenous line:** The temporary placement of an intravenous line may cause discomfort when inserting the needle, as well as bruising; bleeding; and rarely, infection.
- **Hepatitis Testing:** Being tested for Hepatitis may cause anxiety regardless of the test results. Receiving positive results may make you very upset. If your test is negative, there is still the possibility that you could be infected with the Hepatitis virus and test positive at some time in the future. There is always the possibility that the test results could be wrong.
- **Hepatitis B Reporting:** California regulations require laboratories to report new cases of Hepatitis B infection to the county public health department. The reports include the patient's name, social security number, and other identifying information. Information about these new infections is used to track the disease statewide and nationwide. Other than this required reporting, your results will be treated confidentially by the study staff. Personal identifying information will not be reported to other departments or agencies.
- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope PEGPH20, nab-paclitaxel and gemcitabine will be more useful against cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about this treatment combination as a treatment for pancreatic cancer. This information could help future cancer patients as well.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Halozyme Therapeutics
- Researchers and offices at UCSF and UCLA that oversee research
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

What are the costs of taking part in this study?

Halozyme Therapeutics is providing the study drug, PEGPH20, at no cost to you. The costs of nab-paclitaxel and gemcitabine will be billed to you or your insurer.

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. Any procedures done only for research will not be charged to you or your insurer. There is a possibility that your insurer may not cover standard medical care costs because you are in a research study or because you are receiving medical services out of network.

Before you agree to be in this study, you may want to contact your healthcare payer/insurer to see if your plan will cover the costs required as part of your participation. You may request more information about the costs of participating in this study and discuss this with the study team.

If you have any questions, your doctor and the study team will be able to provide you with answers.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Will I be paid for taking part in this study?

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

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Drs. Tempero, and Ko, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her

██████████.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California or the study sponsor ██████████, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) ██████████.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

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.

OPTIONAL ADDITIONAL RESEARCH

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part

in these additional studies if you want to. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Use of Tissue for Research

About Using Tissue for Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Is Tissue Used for Research" to learn more about tissue research.

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While UCSF Medical Center may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, put your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

YES	NO
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2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

YES	NO
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3. Someone may contact me in the future to ask me to take part in more research.

YES	NO
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CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date

Participant's Signature for Consent

Date

Person Obtaining Consent

Date

Witness – Only required if the participant is a non-English speaker