FOX CHASE CANCER CENTER
TEMPLE HEALTH

INFORMED CONSENT DOCUMENT

Phase II study of TAK-228 (MLN0128) in soft tissue sarcomas with dysregulation of the mTOR pathway

Supported by: Millennium Pharmaceuticals, Inc.

Principal Investigator: Margaret von Mehren, MD

Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family, friends or family doctor before you decide to take part in this research study.

You are being asked to take part in this research study because you have soft tissue sarcoma, a type of cancer which starts in soft tissues of the body.

The sponsor of this study is Fox Chase Cancer Center.

Why is this research study being done?

The purpose of this research study is to test if TAK-228 is safe and effective in treating patients with soft tissue sarcoma.

The study drug, TAK-228 has not been FDA approved but it has been shown to prevent tumor growth in animals and is currently being tested in humans.

We do not know if you will benefit from this research study. It is possible that your condition will get better, but it is also possible that there will be no effect on your condition or that your condition will get worse. We can use what we learn from this research study to help other people with the same disease.

How many people will take part in this research study?

Up to 24 people will take part in this research study.

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

Screening before you begin the research study

You will need to have the following exams, tests or procedures to find out if you can be in the research study. These exams, tests or procedures are part of regular cancer care and may be

done even if you do not join the research study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- We will ask you about your medical history and medicine you are taking
- We will do a physical exam which will include height, weight and vital signs
- We will ask about your ability to do your daily activities
- Routine blood tests (1 tablespoon)
- Routine urine test
- Blood pregnancy test (2 teaspoon), if you are a female and able to become pregnant.
- We will evaluate your cancer by doing a CT scan or MRI
    - A CT scan is a computerized x-ray that gives your study doctor pictures of the inside of your body.
    - MRI is a test that uses magnetic field and radio waves to take pictures of the inside of your body.
- We will check your heart by performing an EKG.
    - EKG is a test to measure the electrical activity of your heart
- Perform a biopsy to obtain a tumor tissue sample (this will not be required if you have a sample from a previous biopsy).

During the research study
If the exams, tests and procedures show that you can be in the research study, and you choose to take part, then you will take study treatment and you will need some tests and procedures.

- You will receive the study drug every day of a 21 day cycle until your disease gets worse.

  Note: you will need to take the study drug once daily at approximately the same time each day. You should refrain from eating and drinking (except for water and other prescribed medications that your doctor may have indicated) for 2 hours before and 1 hour after each dose.

  You should avoid contact with the powder in TAK-228 capsules. Do not crush or chew the TAK-228 capsules. Should TAK-228 powder release from a capsule, avoid contact with your skin, ears, nose, and mouth. The area should be thoroughly washed with water if such contact occurs.

  People taking the study drug are asked to drink plenty of liquids to maintain normal hydration. You should tell your doctor if you are having trouble eating or drinking normally or if you have diarrhea or stomach upset.

- We will ask you about the medicine you are taking
- We will do a physical exam which will include weight and vital signs
- We will ask about your ability to do your daily activities
- Routine Blood tests (1 tablespoon).
- Routine urine test
- Blood pregnancy test (1 teaspoon), if you are a female and able to become pregnant.
- Home blood glucose monitoring: You will receive a glucometer for monitoring your blood glucose level at home. The study staff will instruct you how to do home glucose monitoring. You will need to measure your pre-dose fasting blood glucose level and

record the values in your dairy. If your blood glucose level is more than or equal to 150mg/dL, you need to notify the study staff immediately. There is minimal risk associated with the blood glucose test. There is a chance of infection if you share the finger-stick device with someone else.

- We will check your heart by performing an EKG.
- We will ask you about any side effects you may be experiencing
- We will evaluate your cancer by doing a CT scan or MRI

Possible use of a port

If the doctors or nurses cannot draw blood or give you medicine through your veins, you may be asked to have minor surgery to place an "indwelling catheter port" into a large vein in your chest. Medical staff will use the "port" to give you medicines and to draw blood. You will be asked to sign a separate consent form for this procedure, and the "port" will not be used unless you agree. If a port is necessary and you do not agree to its use, you may be unable to continue as part of the research study.

After you stop taking the study drug

End of Treatment Follow-Up

About 30 days after your last dose of study drug, you will need following exams.

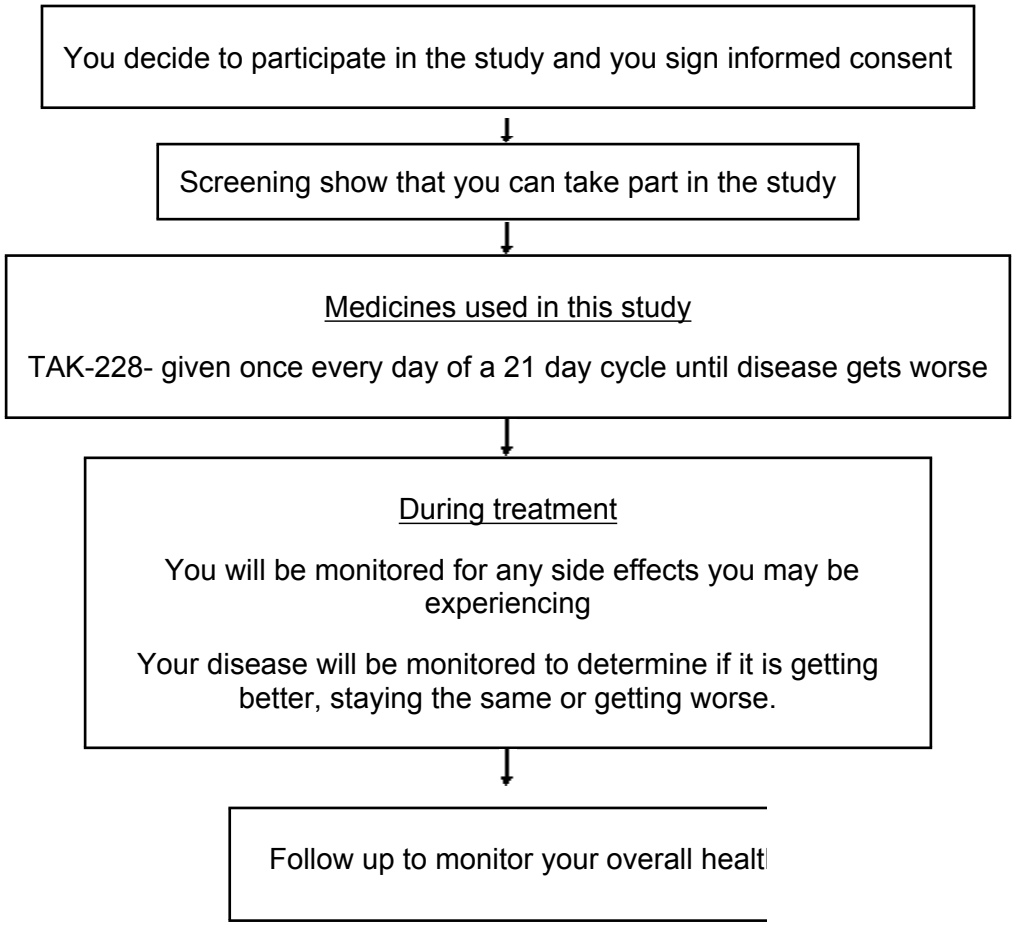
- We will ask you about the medicine you are taking
- We will do a physical exam which will include weight and vital signs
- We will ask about your ability to do your daily activities
- Routine Blood tests (1 tablespoon).
- Routine urine test
- We will check your heart by performing an EKG.
- We will ask you about any side effects you may be experiencing
- We will evaluate your cancer by doing a CT scan or MRI

Follow-Up

After you are finished taking the study drug, we would like to follow up with you for the rest of your life to monitor your overall health. We would like to do this by calling you on the telephone every 3 months.

Study Plan

Another way to find out what will happen to you during the research study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will you be in the research study?

You will be asked to take the study drugs until your disease gets worse or you experience intolerable side effects. After you stop taking TAK-228, the study doctor will follow up with you for the rest of your life to monitor your overall health.

Can you stop being in the research study?

Your participation in this research is completely voluntary. If you agree to participate now and change your mind later, you may withdraw 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 safely and will discuss with you options for withdrawl such as continuing to provide further data collection from routine medical care.

It is important to tell the study doctor if you are thinking about stopping so any risks from the TAK-228 can be evaluated by your doctor. Another reason to tell your doctor that you are

thinking about stopping is to discuss what followup care and testing could be most helpful for you.

Can you be removed from this research study?

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

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

You may have side effects while on the research study. Everyone taking part in the research 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 Tak-228. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

Some deaths have occurred in current human studies: one patient receiving TAK-228 died unexpectedly due to ventricular fibrillation (an abnormal heart rhythm) and cardiac arrest (the heart stops working), events that were assessed as related to TAK-228. With the limited experience we have with TAK-228, we have not determined whether TAK-228 is directly associated with these problems. Other patients receiving TAK-228 have died due to problems related to their cancer, which were not related to taking TAK-228.

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

Risks and side effects related to Tak-228 include those which are:

Most Common (more than 30%)

- High blood sugar (symptoms may include increased hunger, increased thirst, dry mouth and increased urination)
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Decreased appetite
- Diarrhea (increased frequency of bowel movements with loose, watery stools)
- Fatigue
- Irritation to the lining of your mouth, or mouth sores

Very Common (between 10% and 30%)

- Skin irritation, including rash and itching
- Increased weakness
- Change of taste
- Headache
- Anemia (decrease in the number of red blood cells) which may make you feel tired or weak
- Dry mouth
- Pain in the stomach

- Urinary tract infection (symptoms may include pressure, frequency urinating, urgency to urinate, or a burning sensation while urinating)
- Constipation (difficulty having a bowel movement)
- Fever
- Back pain
- Trouble Breathing
- Dehydration or excessive water loss
- Increased creatinine (this may or may not be a sign of damage to your kidney)
- Changes in the electrolytes (such as potassium, magnesium or phosphates) in the blood
- Weight loss
- Cough
- Dizziness (a feeling of light-headedness)

Other potential risks

- Decreased platelet counts. Platelets are important in stopping bleeding. A low platelet count can increase the time to form a blood clot.
- Increase in liver function tests (this may or may not be a sign of damage to your liver; you may not notice any symptoms)
  Inflammation (irritation) of the lungs which may cause shortness of breath and low oxygen levels. Your doctor will monitor you for this.

Radiation Risk for Diagnostic Imaging

- It is unlikely that there will be any harmful effects from the radiation exposure you will receive from participating in this study.
- At high levels of exposure, scientists agree that radiation can cause cancer.
- At low exposure levels most scientists agree that the risk, if any, is very low. You will have low levels of radiation exposure with diagnostic imaging procedures.
- Risks from exposure to radiation may accumulate over a lifetime.

Blood Draw Risks

- Fainting
- Bleeding
- Bruising at the place on your arm where the blood was drawn or needle inserted
- Pain
- Swelling
- Infection (rare)

Biopsy Risks (when applicable)

- Bleeding
- Pain
- Infection, which can be life-threatening or fatal in rare cases

Reproductive Risks

- Study treatments may make you sterile (unable to have children).
- The drugs in this study may affect a baby, before or after the baby is born.
- You should not become pregnant or father a baby while on this research study because the drugs you take could possibly hurt an unborn baby.

- If you are pregnant now or if you are breast-feeding now, you may not take part in this research study.
- If you become pregnant while you are on the research study, you may not continue to take part in the research study.

For women who can become pregnant:

- You should not become pregnant while you are in this study.
- You should not breast-feed your baby while taking drugs for this research study.
- If you are having sex that could lead to pregnancy, you should use birth control during the study and for at least 3 months after the end of study treatment.

For men:

- You should not make a woman pregnant while you are in this study.
- If you are having sex that could lead to pregnancy, you should use birth control during the study and for at least 4 months after the end of study treatment.

For women and men:

- Check with the study doctor about birth control methods. Some methods might not be approved for use in this study.

Precautions and Restrictions

The use of live vaccine and close contact with those who received live vaccines should be avoided during treatment with study drug. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guerin, yellow fever, varicella and TY21a typhoid vaccines.

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 that Tak-228 will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about Tak-228 as a treatment for cancer. This information could help future cancer patients.

What other choices do you have if you do not take part in this research 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.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be 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:

- Fox Chase Cancer Center and affiliated Joint Centers, The Institutional Review Boards of The Fox Chase Cancer Center and Temple University, Temple University, Temple University Health system, Inc., and its affiliates or subsidiaries and other authorized representatives of these organizations.
- Millennium Pharmaceuticals, Inc.
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

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.

You will be given a separate form to review regarding the steps we will take to guard your privacy as part of your participation in the research study. By signing that additional authorization, you will be providing your consent to use and disclose information described in that form connected with your participation in this research study.

What are the costs?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Millennium Pharmaceuticals, Inc. will supply the TAK-228 at no charge while you take part in this study. Millennium Pharmaceuticals, Inc. does not cover the cost of getting TAK-228 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the TAK-228 for some reason. If this would occur, no one will be able to get more and the study would close.

If a problem with getting TAK-228 occurs, your study doctor will talk to you about these options.

If your insurance will not pay for medicines you may need to help with side effects, you may have to pay for them.

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 you be compensated?

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

Your participation in this study may result in discoveries or products that may have commercial value. If there is a commercial value, you will not receive any compensation from the discoveries or products.

What if I get hurt or sick while I am in the study?

If you are injured as a result of your participation in this research study, seek immediate medical care. Temple University Health System or its subsidiaries will treat the injury, though there is no commitment to provide monetary compensation or free medical care. Other financial compensation (such as lost wages or pain and suffering) for such injuries is not available. 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.

What are your rights if you take part in this research study?

Taking part in this research study is your choice. You may choose either to take part or not to take part in the research 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.

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.

New findings

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.

Who can answer your questions about the research study?

Important Contact Numbers	
If you have questions about:	Please Call:
This study, including if you get sick or hurt	Dr. Margaret von Mehren at 215-728-4300
If you have a concern or complaint	Risk Management Department at 215-728-2591
Your rights as a research participant on this study	FCCC Institutional Review Board at 215-214-3754
Your bills or health insurance coverage	Clinical Trial Financial Counselor at 215-214-3768

Where can you get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI website at http://cancer.gov

- For NCI's clinical trials information, go to: http://cancer.govclinicaltrials/
- For NCI's general information about cancer, go to: http://cancer.gov/cancerinfo/

Signatures

By signing below, you tell us that you have gotten all of the information you need; that you have received clear answers to your questions, and that you agree to take part in the research study. You will receive a copy of this form. You may also request a copy of the research plan.

Signature of Participant	**Print Name of Participant**	**Date**

By signing this form the Physician obtaining consent indicates that the research participant has been fully informed of all aspects of the research study.

Signature of Physician Obtaining Consent	**Print Name of Physician Obtaining Consent**	**Date**

By signing this form the person obtaining consent indicates that the research participant has been fully informed of all aspects of the research study.

Signature of Person Obtaining Consent	**Print Name of Person Obtaining Consent**	**Date**

Signature of Legally Authorized Representative (LAR)	**Date**

Print Name of LAR	**Relationship of LAR to Participant**

(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under the Commonwealth of Pennsylvania)