Study Title for Study Participants: Testing MLN0128 (TAK-228) in Advanced Pancreatic Neuroendocrine Tumors that are no longer responding to Rapalog

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

This is a clinical trial, a type of study. Your doctor 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 taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation.

What is the usual approach to my advanced pancreatic neuroendocrine tumor?

You are being asked to take part in this study because you have an advanced pancreatic neuroendocrine tumor (PNET) that is no longer responding to rapalog therapy, such as everolimus.

People who are not in a study are usually treated with either surgery, radiation, or with FDA approved drugs. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

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

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to test any good and bad effects of the study drug MLN0128 (TAK-228) in patients with advanced pancreatic neuroendocrine tumors (PNET) that are no longer responding to rapalog. MLN0128 (TAK-228) could shrink your cancer but it could also cause side effects. Researchers hope to learn if MLN0128 (TAK-228) will shrink the cancer by at least one-quarter compared to its present size. MLN0128 (TAK-228) is an experimental drug which means that the Food and Drug Administration has not approved it

for prescription use outside of a clinical trial. MLN0128 (TAK-228) blocks the activity of a specific protein in the body called mTOR, which controls cell growth. As an mTOR inhibitor, MLN0128 (TAK-228) may interfere with the creation of mTOR and possibly slow or stop tumor cells (cancers) from growing and living. There will be about 40 people taking part in this study.

What are the study groups?

All study participants will get the same study drug, MLN0128 (TAK-228). You will take MLN0128 (TAK-228) by mouth daily at the same approximate time for the entire cycle (28 days). Each dose will be a 3 mg capsule. MLN0128 (TAK-228) will be administered on an empty stomach. You should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose. You must not consume food or beverages containing grapefruit or Seville oranges 7 days before the first dose of study drug and throughout the study.

MLN0128 (TAK-228) should be swallowed whole (not chewed) with one 8 ounce glass of water. You should take your dose of MLN0128 (TAK-228) at approximately the same time each day without food. If you miss a dose (if it is not taken within 12 hours after the scheduled dosing time) or vomit up the capsules of MLN0128 (TAK-228), you should skip that dose and start your dosing with the next scheduled dose. You will not be allowed to make up missed doses. You will need to bring any extra remaining capsules with you to each clinic visit. You will be required to maintain a medication diary and bring it with you to every clinic visit.

How long will I be in this study?

You will receive the study drug as long as your cancer does not get worse, the side effects are tolerable, and you agree to stay on study. When you finish taking MLN0128 (TAK-228), your doctor will continue to watch you for side effects and follow your condition with telephone calls for follow-up exams every 3 months for 2 years and every 6 months for the third year from your enrollment in the study. You will be followed for survival for 5 years from the date of study registration.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra exams and testing to find out if you can be in the study:

- You will need to have the following blood tests: fasting blood sugar, lipid profile, and HbA1C (provides an overall picture of what your average blood sugar levels have been other a period of weeks/months)

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra testing. They are not part of the usual approach for your type of cancer.

During the study:

- You will need to have the following blood tests monthly while on study: fasting blood sugar, lipid profile, and HbA1C
- Monitor your blood sugar

Before starting treatment with MLN0128 (TAK-228), you will be provided an in-home glucometer and supplies to monitor your blood sugar, because there in an increased risk of elevated blood sugars with treatment. This will be provided to you free of charge. You will be trained on proper use of the glucometer and instructed to collect a daily finger stick blood sugar level before eating each morning. You should bring your glucometer with you to each study visit so that the data collected can be reviewed and recorded.

You should contact your study nurse immediately if the blood sugar is abnormal (that is ≥ 150 mg/dL) for further instructions. High blood sugars observed during home glucose monitoring should be confirmed by the study team in the clinic. If no irregularities in the fasting blood sugar level are observed after two months, then the frequency of blood sugar testing can be reduced to once weekly. You should continue to notify your study nurse for fasting blood sugar levels that exceed 150 mg/dL. If your blood sugar levels are not well controlled, you may require temporary use of medicines to lower your blood sugar with continued frequent testing of you blood sugar levels.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The drug used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug. These risks are described in more detail below.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Some deaths have occurred in current human studies: one patient receiving MLN0128 (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 MLN0128 (TAK-228). With the limited experience we have with MLN0128 (TAK-228), we have not determined whether MLN0128 (TAK-228) is directly associated with these problems. Other patients receiving MLN0128 (TAK-228) have died due to problems related to their cancer, which were not related to MLN0128 (TAK-228).

Possible Side Effects of MLN0128 (TAK-228)

COMMON, SOME MAY BE SERIOUS In 100 people receiving MLN0128 (TAK-228), more than 20 and up to 100 may have:
• Constipation, diarrhea, nausea, vomiting • Sores in the mouth which may cause difficulty swallowing • Tiredness • Loss of appetite • Itching, rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MLN0128 (TAK-228), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Dry mouth • Heartburn • Swelling of the body

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MLN0128 (TAK-228), from 4 to 20 may have:
• Fever • Infection which may cause painful and frequent urination • Bruising, bleeding • Weight loss • Dehydration • Dizziness, headache • Changes in taste • Difficulty sleeping • Kidney damage which may require dialysis • Cough, shortness of breath

RARE, AND SERIOUS In 100 people receiving MLN0128 (TAK-228), 3 or fewer may have:
• Heart stops beating • Abnormal heartbeat which may cause fainting • Change in the heart rhythm • Damage to the lungs which may cause shortness of breath

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

You should report and discuss with your study doctor any other medication(s) you are taking while you are treated with the study drug, so he/she can take action to prevent any possible drug interactions. You should avoid Seville oranges, grapefruit, herbal supplements and St John's wart while on study. Please refer to the drug interaction handout and wallet card for additional information.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study and for up to 17 weeks (120 days) after you have finished this study. The drug used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. It is important that you understand that you need to either practice "abstinence" (that is avoiding sexual activity) or use birth control while on this study.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an appropriate double barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), sponge and

spermicide, in addition to the male use of a condom) or involve female use of prescribed "birth control pills" or a prescribed birth control implant. Both double barrier contraception and birth control pills or implants must be used for at least one week prior to the start of the study and continuing for 90 days after the last dose of the study drugs for women study participants and 120 days for men study participants. If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing unborn baby

If a woman becomes pregnant while on this study or within 12 weeks after the last dose of study drug, she will be asked information concerning the outcome of her pregnancy. If a female partner of a male patient becomes pregnant while the male patient is on the study or within 16 weeks after the last dose of study drug, the male patient must notify the investigator.

What possible benefits can I expect from taking part in this study?

This study has only a small chance of helping you because we do not know if the study drug is effective. This study may help researchers learn things that may help other people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

What are the costs of taking part in this study?

MLN0128 (TAK-228) will be supplied at no charge while you take part in this study. It is possible that the MLN0128 (TAK-228) may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of study drug preparation and administration (if any), and tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are being done at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

No funds have been set aside to compensate you in the event of injury.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

The ECOG-ACRIN Cancer Research Group is carrying out this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the U.S. Department of Health and Human Services (DHHS). With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes. There are organizations that may inspect your records.

There are organizations that may inspect your records. These organizations are required to

make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- Montana Cancer Consortium
- The study sponsor, ECOG-ACRIN, any drug company supporting the study
- Southwestern Oncology Group (SWOG), Alliance for Clinical Trials in Oncology (ALLIANCE), NRG Oncology.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact information for your study doctor is listed on the consent cover page.

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)