FOX CHASE CANCER CENTER
TEMPLE HEALTH

FOX CHASE CANCER CENTER
AT TEMPLE UNIVERSITY HOSPITAL
All hospital services provided by Temple University Hospital

INFORMED CONSENT DOCUMENT

GI-094: A Pilot Phase II, single arm, open-label, investigator-initiated clinical trial of Regorafenib plus 5- Fluorouracil/Leucovorin (5-FU/LV) beyond progression on Regorafenib monotherapy in metastatic colorectal cancer (mCRC)

Principal Investigator: Namrata Vijayvergia, MD
Temple University Hospital/Study Site Investigator: Juhi Mittal, MD

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

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 discusses 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 metastatic colorectal cancer and your cancer progressed when you were treated with Regorafenib monotherapy. Metastatic means that your cancer has spread to other parts of your body.

The sponsor of this study is Fox Chase Cancer Center. Namrata Vijayvergia, MD, is the sponsor-investigator for this study

Why is this research study being done?

The purpose of this research study is to determine whether a combination therapy of Regorafenib and 5-fluorouracil (5FU)/ Leucovorin (LV) will result in control of your metastatic colorectal cancer. Regorafenib and 5FU combination therapy is not yet approved for treatment of metastatic colorectal cancer in humans by FDA. There is some clinical evidence that suggests the combination therapy could be beneficial for treating metastatic colorectal cancer.

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?

About 15 people will take part in this research study.

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

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.

- A review of your medical history and any medications you are currently taking or have taken in the past
- Physical examination including vital signs, weight and height
- You will be asked how cancer effects your daily activities
- Blood pregnancy test (2 teaspoons) within 3 days prior to registration, if you are a woman and are able to become pregnant.
- Routine blood test (1 tablespoon)
- Urine test
- We will perform EKG to check how your heart is functioning
- We will ask you about any side-effects that you may be experiencing from previous treatments
- A CT scan or MRI scan of your tumor
  - A CT scan is a computerized X-ray that gives your study doctor pictures of the inside of your body
  - A MRI scan uses a magnetic field and radio waves to take pictures of the inside of your body

During the research study

Study Treatment

The drugs in this study will be administered in cycles. Each cycle is of 28 days and when one cycle ends the next cycle begins. During the study you will receive the following drugs to treat your cancer.

- Regorafenib to be taken orally, once daily for 21 days.
- 5FU will be administered at the clinic intravenously on day 1 and day 15 of each cycle.

The treatment will go on as long as you continue to derive benefit from it, that is, your cancer is getting better or does not progress. The treatment will stop if your cancer gets worse or you have severe side-effects or if in your Physician's opinion it is best for you to discontinue from the

study. We will evaluate how you are responding to the treatment by performing MRI or CT scan of your tumor every 2 cycles (8 weeks).

Tests and Procedures

If the exams, tests and procedures show that you can be in the research study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care. They are being done more frequently because you are in this research study.

- We will ask you about all the medicines that you are taking
- We will perform physical examination including vital signs and weight
- We will ask you how cancer effects your daily activities
- Routine blood test (1 tablespoon)
- Urine test
- We will ask you if you are experiencing any side-effects due to the treatment
- An MRI or CT scan of your tumor

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.

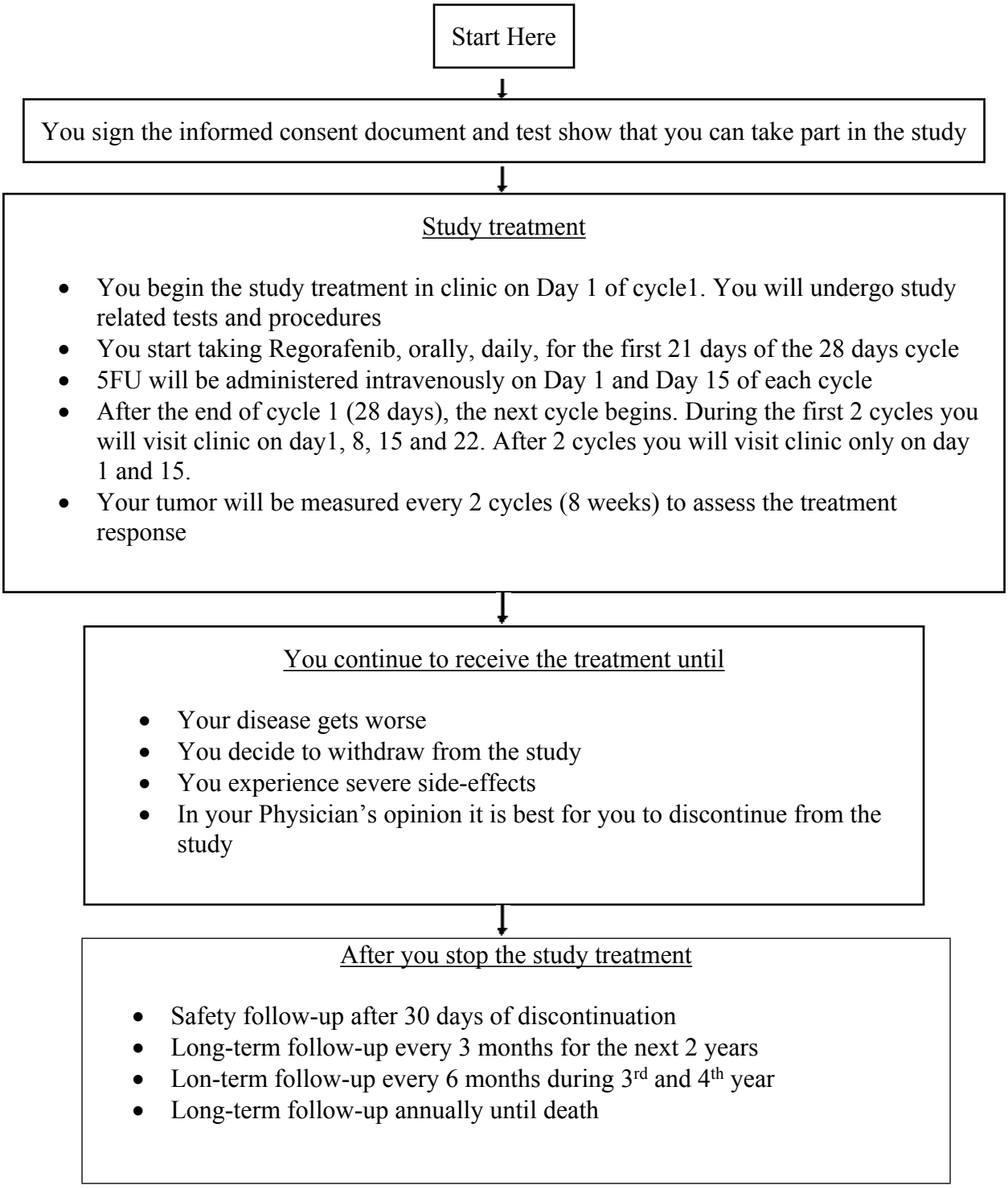
After you have finished study treatment

We will perform a safety follow-up after 30 days of the discontinuation of the treatment. In this follow-up visit we will:

- Ask you about the medication that you are taking
- Perform a physical examination including vital signs, and weight
- We will ask you how cancer affects your daily activities
- Routine blood test (1 tablespoon)
- Urine test
- We will ask you about any side-effects that you may be experiencing due to the study treatment

We will continue to follow-up with you after the safety follow-up every 3 months for the next 2 years, every 6 months during 3rd and 4th year and then annually until death. During this follow-up your tumor may be monitored by MRI or a CT scan.

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.


Start Here
You sign the informed consent document and test show that you can take part in the study
Study treatment
• You begin the study treatment in clinic on Day 1 of cycle1. You will undergo study related tests and procedures
• You start taking Regorafenib, orally, daily, for the first 21 days of the 28 days cycle
• 5FU will be administered intravenously on Day 1 and Day 15 of each cycle
• After the end of cycle 1 (28 days), the next cycle begins. During the first 2 cycles you will visit clinic on day1, 8, 15 and 22. After 2 cycles you will visit clinic only on day 1 and 15.
• Your tumor will be measured every 2 cycles (8 weeks) to assess the treatment response
You continue to receive the treatment until
• Your disease gets worse
• You decide to withdraw from the study
• You experience severe side-effects
• In your Physician's opinion it is best for you to discontinue from the study
After you stop the study treatment
• Safety follow-up after 30 days of discontinuation
• Long-term follow-up every 3 months for the next 2 years
• Lon-term follow-up every 6 months during 3rd and 4th year
• Long-term follow-up annually until death

How long will you be in the research study?

You will be asked to take Regorafenib and 5FU until your cancer gets worse or you have unacceptable toxicity or your doctor thinks it is best for you to stop being in the study. After you are finished taking the study treatment, the study doctor will ask you to visit the office for follow-up exams after 30 days of discontinuation and then every 3 months for the next 2 years and every 6 months for the 3rd and 4th year and then annually until death.

Can you stop being in the research study?

Yes. You can decide to stop at any time. 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 withdrawal such as continuing to provide further data collection from routine medical care.

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 regorafenib and 5FU**.** In some cases, side effects can be serious, long lasting, or may never go away. In rare but serious circumstances there is also a risk of death.

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 the regorafenib include those which are:

Likely (>20%)

- Fatigue (feeling of being overly tired and lacking energy)
- Weakness
- Palmar-Plantar Erythrodyesthesia (Hand-Foot-Syndrome) Redness, tenderness, pain and possible peeling of the palms of the hands and soles of the feet. The redness looks like a sunburn. The affected area can become dry and peel with numbness or tingling developing
- Rash
- Diarrhea (increased frequency of bowel movements with loose, watery stools)

- Mucositis/stomatitis- sores in the lining of your mouth and/or throat that can be painful and make it hard to swallow
- Loss of appetite
- Weight loss
- Hypertension (high blood pressure) Symptoms may include headache, dizziness, palpitations, blurred vision, ringing in the ears and nose bleeds
- Voice changes/hoarseness/difficulty forming sound
- Thrombocytopenia (low platelet count) – platelets are important in stopping bleeding. A low platelet count can increase the time to form a blood clot
- Leukopenia/Neutropenia (low white blood cell count) – a low white blood cell count makes it hard for you to fight infections
- Hypocalcemia (low calcium levels in the blood) Symptoms of a low calcium level may include numbness and tingling in the hands and feet, muscle cramps, twitches and spasms, fatigue, confusion, disorientation and seizures.
- Hyponatremia (low sodium levels in the blood) Symptoms may include nausea and vomiting, loss of appetite, headache, confusion, fatigue, restlessness and irritability, muscle weakness, spasms or cramps, decreased consciousness, seizures or coma.
- Low blood levels of phosphorous (can affect your bones, muscles, heart, and central nervous system)
- Increased blood levels of the pancreas enzyme called lipase
- Increased levels of protein in the urine- this may a sign of kidney damage

<u>Less Likely</u> (5-19%)

- Headache
- Fever
- Infection
- Bleeding
- Hair loss
- Altered taste
- Dry mouth
- Pain
- Muscle stiffness
- Anemia (low hemoglobin, low hematocrit or low red blood cell count) – red blood cells carry oxygen and nutrients throughout the body. Symptoms that may be experienced as a result of low red blood cell counts may include feeling tired and weak, shortness of breath, increased heart rate, dizziness or lightheadedness, headache, chest pain and pale skin.
- Hypokalemia (low levels of potassium) Symptoms may include muscle weakness, cramping, leg discomfort, an irregular heart beat and confusion
- Elevated liver enzymes: Liver enzymes, proteins made by the liver, indicate how well your liver is functioning. High liver enzyme levels may cause you to feel overly tired or weak, you may bruise or bleed more easily, and you may experience abdominal pain or have a yellowing of the skin or eyes
- Hyperbilirubinemia (elevated bilirubin levels in the blood) Bilirubin is a chemical that is released when red blood cells are broken down. Bilirubin is used by the liver to make

bile. Symptoms of elevated bilirubin levels include a yellowing of the skin, eyes and mucous membranes.
- Low thyroid hormone production, which may cause symptoms including tiredness, depression, weight gain, cold intolerance, dry coarse hair, difficulty having bowel movements, dry skin, muscle cramps, high cholesterol, trouble with concentration and swelling of the legs.

<u>Rare but serious</u> (< 5%)

- Delay in wound healing or breakdown of a wound that has healed
- Gastrointestinal (GI) perforation which is the development of an opening or hole in the wall of the bowel or stomach (gastrointestinal tract) that may require surgery to repair and can be life threatening
- Fistula- breakdown in the surgical connection between two pieces of bowel
- Reversible Posterior Leukoencephlopathy Syndrome (RPLS): a neurological disorder which can present with a headache, confusion, seizures, or vision changes
- Heart attack

Risks and side effects related to the 5-fluorouracil (5-FU) includes those which are:

<u>Likely</u> (>20%)

- Diarrhea – increased frequency of bowel movements with loose watery stools
- Abdominal pain
- Anemia (low hemoglobin, low hematocrit or low red blood cell count) – red blood cells carry oxygen and nutrients throughout the body. Symptoms that may be experienced as a result of low red blood cell counts may include feeling tired and weak, shortness of breath, increased heart rate, dizziness or lightheadedness, headache, chest pain and pale skin
- Leukopenia/Neutropenia (low white blood cell count) – a low white blood cell count makes it hard for you to fight infections
- Thrombocytopenia (low platelet count) Platelets are important in stopping bleeding. A low platelet count can increase the time to form a blood clot, causing you to bruise or bleed more easily
- Nausea – feeling sick to your stomach
- Vomiting – throwing up
- Mucositis/stomatitis – sores in the lining of the mouth and/or throat that can be painful and make it painful or hard to swallow
- Photosensitivity – skin sensitivity to the sun causing a painful rash and burn
- Loss of appetite

<u>Less Likely</u> (5-19%)

- Hair loss
- Dry itchy and cracked skin
- Darkening of nail beds and the vein where the drug was infused.

- Nail loss
- Palmar-Plantar Erythrodyesthesia (Hand-Foot-Syndrome) – redness, tenderness, pain and possible peeling of the palms of the hands and soles of the feet. The redness looks like a sunburn. The affected area can become dry and peel with numbness or tingling developing.
- Headache
- Confusion
- Changes in vision
- Nose bleeds
- Chest pain
- Shortness of breath
- Irritation and/or tearing of the eyes
- Irritation of the veins

Rare but serious (< 5%)

- Heart attack – symptoms may include chest pain/tightness, shortness of breath, nausea, sweating and dizziness
- Hypersensitivity Reaction (allergic Reaction) – an overactive immune response that results in local tissue injury or other changes throughout the body in response to a foreign substance or drug. Symptoms of an allergic reaction may include fever, fast heart rate, rash, hives, swelling, itching, flushing, changes in blood pressure, nausea, chest pain and shortness of breath.
- Anaphylaxis – a severe allergic reactions which can cause shock, low blood pressure and death
- Stomach ulcer/bleeding

Risks and side effects related to the Leucovorin (LV) include those which are:

Likely (>20%)

- Fatigue – feeling of being overly tired and lacking energy
- Nausea – feeling sick to your stomach
- Vomiting – throwing up
- Diarrhea – increased frequency of bowel movements with loose, watery stools
- Rash
- Itching

Rare but serious (< 5%)

- Hypersensitivity Reaction (Allergic Reaction) – an overactive immune response that results in local tissue injury or other changes throughout the body in response to a foreign substance or drug. Symptoms of an allergic reaction may include rash, hives, swelling, itching, flushing, changes in blood pressure, nausea, chest pain and shortness of breadth

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 at the needle insertion site
- Swelling
- Infection (rare)

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.

For men:

- You should not make a woman pregnant while you are in this study.

For women and men:

- If you are having sex that could lead to pregnancy, you should use birth control while you are in this study.
- Check with the study doctor about birth control methods and how long to use them. Some methods might not be approved for use in this study.

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 the regorafenib and 5FU combination therapy 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 the regorafenib and 5FU combination therapy 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.
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Bayer Pharmaceuticals-supplier of the study drug Regorafenib

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.

Bayer will supply regorafenib at no charge while you take part in this study. Bayer does not cover the cost of getting regorafenib 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 regorafenib to Bayer. If this would occur, other possible options are:

- You might be able to get regorafenib from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no regorafenib available at all, no one will be able to get more and the study would close.

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

5FU is commercially available and will be billed to you in the same way you are usually billed for medicines.

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.

What if you are injured while taking part in this research 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.

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 are enrolled at the Fox Chase location (333 Cottman Ave)	
If you have questions about:	Please Call:
This study, including if you get sick or hurt	Dr. Namrata Vijayvergia 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
If you are enrolled at the Temple University Location (3401 N Broad Street)	
If you have questions about:	Please Call:
This study, including if you get sick or hurt	Dr. Juhi Mittal at 215-707-2777
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	Social Work Department at 215-707-7569

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/

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)