This informed consent applies to patients older than 18 years of age, with stage I, II or III cancers at high risk of metastatic recurrence.

Name of participant:_____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have completed all your planned treatments for your cancer. Because of the type of cancer you have, you are potentially still at risk of having this cancer come back as a spread cancer in your body ("metastatic recurrence"), sometime in the future. We are proposing a new treatment that might decrease the chances of cancer coming back. It is possible that you may already be cured of your cancer before you receive this study drug, but we do not yet know that. In this study, you will receive either IFETROBAN or Placebo (a pill that looks like IFETROBAN but has no actual medicine in it). IFETROBAN makes platelets (a type of blood cell that helps you clot when you cut yourself) less "sticky". Because cancer cells can stick to platelets and then ride on them to get to different parts of the body, we believe that IFETROBAN may help delay and even cut down the chance of cancer spreading to other parts of the body, however it is not known at this time if IFETROBAN will treat your cancer. We hope to find new information that will help us improve treatments for cancers like yours. In laboratory work with animal models, we have seen a reduction in the rate of metastasis and hope that this will also happen in humans.

The purpose of this study is to determine if IFETROBAN is safe, practical to take, and if it delays or reduces the chance that cancer will spread to other parts of the body. IFETROBAN is investigational which means it is being tested in research studies and has not been approved by the U.S. Food and Drug Administration (FDA). We will do a thorough study of the side effects that everybody in this study has while taking these drugs. We will check if your cancer has come back or not throughout the study. If we see too many side effects, we will lower the dose of the study drugs. We think about 30 patients will take part in the study at the Vanderbilt University Medical Center.

People participating in the study will be divided in 2 groups. One group will receive IFETROBAN and the other will receive Placebo. A computer will decide by chance whether you will take IFETROBAN or Placebo. You will have 1 in 3 chance that you will get Placebo. Neither you nor your doctor will know which one you are getting. We will compare what happens to each of the two groups of people throughout the study.

IFETROBAN is a drug that is provided for this study by Cumberland Pharmaceuticals Inc. (CPI) and it is licensed by Vanderbilt which means that Vanderbilt could make money on IFETROBAN if it is approved and marketed for sale. This is what is known as an "institutional conflict of interest." Dr. Reid and Vanderbilt University Medical Center are committed to ensuring that their research is conducted with honesty and without bias, so we have put the following safeguards in place to protect against the conflict of interest.

Before the research can begin, the study must be approved by a research expert outside of Vanderbilt. They will review the study to make sure participants are protected from any institutional conflict of interest.

We have appointed a safety board from outside of Vanderbilt University. The board will review the results and safety of the study and advise Dr. Reid if changes need to be made for the safety of study participants.

If you have any questions about the institutional conflict of interest and how it could affect this study, please discuss them with Dr. Reid. Her contact information is in item 12 of this consent, "Who to call for any questions."

2. What will happen and how long will you be in the study?

Before Treatment Starts (Screening)

Before treatment starts, you will undergo a screening process to find out if it is okay for you to be in the study. Most of this screening process is done on all cancer patients whether or not they are taking part in a study.

Treatment Plan

You will be given IFETROBAN or Placebo to take daily. Your dose will be assigned by your doctor. The tablet strengths will be labeled on the bottles given to you.

IFETROBAN or Placebo CAPSULES:

- Please take the capsules at about the same time every day, preferably in the morning (without food – empty stomach, about 30 minutes before a meal or 6 hours after) with a glass of water.
- You should swallow the capsules as a whole and not chew them.
- If you forget to take a dose of IFETROBAN or Placebo and it is within 4 hours of when it should have been taken, you should take the dose. If it has been more than 4 hours, you should skip that dose and take the next dose at the next regular time.
- If you vomit after taking a dose of IFETROBAN or Placebo, you should not make up the dose or take additional pills, you should take the next dose at the next regular time.

Each 4 week period is called a "treatment cycle". If all goes well with a treatment cycle, you will restart a new treatment cycle.

Study Duration and Follow-up

Every 3 months for 12 months: You will return to see your study doctor.

You will keep taking the study treatment until:

- You complete planned treatment (12 months), or
- Your cancer comes back, or
- You get bad side effects from the treatment that you cannot tolerate, or
- You wish to stop the study, or
- If the study is cancelled

You will be closely followed by the research nurse while on study and up to 4 weeks after being off study drugs. At the end of the study, you will visit your study doctor for an **End of Treatment visit**.

For up to a year after you stop taking IFETROBAN or placebo, we will check your medical record to see how you're doing.

Study Procedures - The following describes each of the study procedures in more detail

The following tests and procedures are considered standard of care. This means you would have them even if you were not in this clinical trial. The **routine/standard care tests and procedures** include:

- **Demographics**. We will record your demographic information, including your age, sex, and race/ethnicity
- **History of your medical care**. Your study doctor will ask about what medicines and/or vitamins you are taking now, and what operations you have had.
- **Complete physical examination.** including your performance status which is an assessment of your ability to carry out daily activities
- **Vital signs.** We will measure your height (only at the start of the study), weight, temperature, blood pressure, and heart rate.
- **Blood and Urine tests**. Blood tests will check the levels of white blood cells, red blood cells, and platelets. Blood tests will also tell the levels of sugar, minerals and salts in your body (to make sure your kidneys and liver are working well) and will tell us if you have any risk of bleeding. We will take about 3 tablespoons of blood. For women that can still have children, a serum or urine pregnancy test will be done.

The tests and procedures that are **for research purposes** include:

- **Blood and urine tests for tumor markers.** This is done to understand how the study drug affects some elements and tumor markers in your blood and urine. We will take about 3 tablespoons of blood and 1 cup of urine each time. You don't need to be on an empty stomach to get these blood tests.
- **A questionnaire on your quality of life.** This will take about 10 minutes to complete each time.
- **Pill Diary**. This record keeping aide should take about 1-2 minutes each week. We will give you a supply of pills that will last for the month. We will ask you to keep a pill diary, which will be collected by the study nurse on your clinic visits. This is a simple form where you will write down the times you take your medicine every day. In this diary you will write the date, the time and the number of pills you take, and any new symptoms you have. If you miss any pills, you should also write that in the diary. Your study nurse will give you complete directions for how to keep the diary.

Study Calendar: This table explains when you will have each of these tests and procedures

Each Cycle of treatment lasts 4 weeks or about one month

Parameter	Pre-Treatment[1]	Cycle				End of Treatment[2]	30 days post completion of ifetroban	12 months post completion of ifetroban
		C1 D1	C 1 D15 and C2 D1	C4 D1	D1 of C1, C4, C7, C10			
Demographics	X							
	CLINICAL EVALUATIONS:							
History and Physical	X	X		X	X	X		
Height		X						
Vital signs and Weight		X		X	X	X		
Performance status	X	X		X	X	X		
Chart review for presence or absence of metastatic disease								X
	LABORATORY EVALUATIONS:							
Hematology (CBC/diff, plt)	X	X	X	X				
Comprehensive Metabolic Panel[5]	X	X	X	X		X		
Pregnancy Test[4]	X							
INR	X		X	X		X		
Platelet Function Screen	X			X				
	TREATMENT ADMINISTRATION:							
Ifetroban or placebo		250 mg PO once daily for 12 months						
	CORRELATIVE STUDIES:							
Blood and urine collection[3]		X		X				
Patient Reported Outcome		X				X		
	ADDITIONAL INFORMATION:							
Concomitant Medications		X (Con Med Review will be assessed throughout the study)						

Review				
Adverse Events Assessment		**X (AE will be assessed throughout the study)**	**X**	

Study Samples

Your samples and information about you may be made available to others to use for research (see section 15. Authorization to Use/Disclose Protected Health Information for more information). To protect your privacy, we will not release your name or other information that could identify you. You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, and/or others. If this happens, there are no plans to provide money to you.

3. Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. Cumberland Pharmaceutical, Inc. will provide the study drug free of charge for your use in this study.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

http://www.cancer.gov/clinicaltrials/learning/insurance-coverage

4. Side effects and risks that you can expect if you take part in this study:

These are the side effects that researchers know about. You may experience none, some or all of those listed below. There might be other side effects that researchers do not yet know about since this drug has not been used before in cancer patients. Please discuss the rate of recurrence of your cancer

with the study doctor. If important new side effects are found, the study doctor will discuss these with you.

a) Ifetroban

Common (> 10% chance)

- None

Less Frequent (1 - 10% chance)

- Myocardial Infarction (heart attack). This occurred in two completed studies of relatively high risk populations, subjects with unstable angina and post-acute myocardial infarction.
- Headache
- Muscle aches
- Bleeding
- Nausea and vomiting
- Stomach pain
- Dizziness

Rare (< 1% chance)

- None

b) Drug Interactions

As with all drugs, there is a chance that some herbal products or medications can affect how the study drugs work. Such herbs and medications include drugs that increase the risk of bleeding, such as aspirin, blood- thinners, Ginkgo biloba, ginseng, etc. These may cause increased risk of bleeding. These herbs or medicines should be avoided while on study. For your safety, you must tell the study doctor or nurse about all the drugs you are taking, including over-the-counter drugs and herbals, before you start the study and before taking any new drugs while you are on the study. Your doctor and nurse will make sure that your prescription medications are not going to interfere with the study drugs and vice-versa.

Pregnancy
It is not known if the study drug may harm an unborn child.

If you are a male, you must not be planning to father a child while you are in the study and for 5 months after the last dose of study drug.

If you are female, you must not be pregnant or be breast-feeding, and you must not plan to become pregnant within 5 months after the last dose of study drug. Tell your study doctor immediately if you become pregnant

while taking the study drug or within 5 months after your last dose. You may be asked questions later about the pregnancy and the baby.

If you are a:

- Female of child-bearing potential (not post-menopausal or surgically sterile) not completely abstaining from sex with a male partner who could father children
- Male of child-bearing potential (have not had a vasectomy) not completely abstaining from sex with a female partner who could have children

You and your sexual partner must always use two highly effective forms of birth control to ensure you/your partner do not become pregnant. This should be started from 15 days before you start IFETROBAN, continue while taking the study drug, and for 5 months after the last dose of study drug. You should talk to your study doctor or nurse about acceptable methods of birth control.

Use a combination of **two** the following:

a) Barrier methods **with** spermicide
- condom (male or female)
- occlusive cap (diaphragm or cervical/vault caps/shield)
- use of two barrier methods is acceptable (i.e. male condom + diaphragm or equivalent)

b) Placement of an intrauterine device (IUD) or intrauterine system (IUS).

c) Hormonal implants or combined oral contraceptives

5. Risks that are not known:

Because the study drug in this trial is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. As with all drugs, there is the chance that there may be unknown or impossible to predict risks that were not known about before. If you have side effects from this treatment, please tell your doctor or nurse about them right away. We will tell you if there is any new information about the drugs used in this study that may affect your decision to stay in the study.

6. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred, then you and/or your insurance may be billed for the cost of medical care provided at Vanderbilt to treat the injury. You will be responsible for any copayments or deductibles associated with the treatment of that injury.

There are no plans for Vanderbilt [or the Sponsor] to pay for the costs of any additional care. There are no plans for Vanderbilt [or the Sponsor] to give you money for the injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study. We hope the information we get in this study will help other patients who get treatment for cancer in the future.

b) The benefits you might get from being in this study. We do not know if you will get any direct help from this drug. IFETROBAN may or may not help you (cut down or delay the risk of your cancer coming back). Therefore, there are no promises that you will get any help from this treatment at all. Since each cancer differs in the chance that it will come back, the benefit you might get from IFETROBAN could also differ depending on the type of cancer you had.

8. Other treatments you could get if you decide not to be in this study:

You cannot get IFETROBAN outside of a research study. Because you have already completed all your planned treatments, there are no other standard of care treatment options at this point in your care (the standard of care is observation – wait and see).

9. Payments for your time spent taking part in this study or expenses:

You will be compensated $25 for each month you complete your pill diary ($25 x 12 = up to $300 total). You will be compensated $25 per blood draw/urine collection (one at baseline, one at 3 months = up to $50 total). You will be compensated $27 for completion of baseline and end of treatment quality of life surveys ($27 total). Thus, if you complete all planned study procedures, you may be compensated up to $377 total. We may ask you for your Social Security number and address before you are compensated for taking part in this study.

10. Reasons why the study doctor may take you out of this study:

You may be taken out of the study if:

- staying in the study would be harmful to you
- you have side effects you cannot tolerate
- you need treatment not allowed in the study
- your cancer comes back
- you fail to follow instructions
- the study is cancelled
- you are a female and you become pregnant

There may be other reasons to take you out of the study that we do not know at this time. If you are taken out of the study, you will be told the reason why, and your doctor will discuss other treatments with you. You will be followed for 4 weeks after stopping study drugs. If you stop taking study drugs due to bad side effects from the treatment that you cannot tolerate, you will be followed until these side effects are better or resolved.

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way. Being in this study is voluntary. You can change your mind about being in this treatment program at any time. Your decision will not affect your future care. Deciding not to be in this study, or stopping participation in it, will cause no penalty or loss of benefits you otherwise would have. You may seek care from a doctor of your choice at any time. If you decide to no longer take part in the study, the study doctor may ask you to allow him/her to follow you and collect information from your medical records, if you agree. You will also be asked t o return to clinic for a last visit to check blood work and your physical well-being.

If you decide to leave the study, please contact Dr. Reid in writing and let her know that you are leaving. Her mailing address is:

[redacted]

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact [redacted]

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Clinical Trials Registry.

A description of this clinical trial will be available on 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.

14. Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Patient records will be stored and maintained in the Clinical Trials Support Services office. Access to these records is limited to Dr. Reid and her study team. Any information that is kept in our electronic database is password protected and has limited employee access. Any research data that has been placed into your research record will be kept for at least 6 years after the study is finished. Any research data that has been put into your medical record will be kept for an unknown length of time.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Sonya Reid and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

15. Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing (“disclosure”) such data must follow federal privacy rules. By signing the consent for this study, you are agreeing (“authorization”) to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Sonya Reid and her study team may share the results of your study and/or non-study linked medical history, exams, lab tests, scans, samples, diaries, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, governmental agencies in other countries where the study drug may be considered for approval, Vanderbilt University medical center, the IRB reviewing the study, the Food and

Drug Administration, study safety monitors and auditors, data managers and other agents and contractors used by the study team, researchers and study team members, representatives of Cumberland Pharmaceutical, Inc., the drug supplier of the study drug in this trial, and its authorized agents, the Scientific Review Committee, the National Cancer Institute, and Insurance Companies for billing purposes. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Sonya Reid in writing and let her know that you withdraw your consent. Her mailing address is: [redacted] At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date	Signature of patient/volunteer

Consent obtained by:

Date	Signature
	Printed Name and Title

Time