UNIVERSITY OF CALIFORNIA LOS ANGELES
CONSENT TO PARTICIPATE IN RESEARCH

Study Title: **A Phase II Randomized Multicenter Placebo- Controlled Blinded Study of Sorafenib Adjuvant Therapy in High Risk Orthotopic Liver Transplant (OLT) Recipients with Hepatocellular Carcinoma (HCC), Protocol dated July 1, 2014**

Lay Title: A study of a drug to prevent recurrence of liver cancer following liver transplantation in patients with liver cancer

INTRODUCTION

Ronald Busuttil, MD, PhD, Fady M. Kaldas, MD, [redacted] and associates from the Department of Surgery at the University of California, Los Angeles are conducting a research study.

The researchers will explain this study to you. **Research studies are voluntary and include only people who choose to take part.** Please take your time about deciding whether to participate in this study. Before deciding:

- You can discuss this study with friends and family.
- You can also discuss it with your health care doctor or request a second opinion.
- If you have any questions, you can ask the researchers for more information before deciding to participate.

The research team is asking you to be in this study because you received a liver transplant and are at a high risk of the liver cancer recurrence after your liver transplant.

WHY IS THIS STUDY BEING DONE?

Hepatocellular carcinoma (HCC)-liver cancer is a significant health problem, accounting for more than 1,000,000 new cases per year world-wide and is the third leading cause of cancer deaths in the world. The incidence of liver cancer is also increasing in the United States and causes about 13,000 deaths yearly. Outcomes for patients with HCC have been historically poor, regardless of treatment.

Liver transplantation is a treatment option for liver cancer patients, but despite transplantation, the HCC (liver cancer) can recur in the new, transplanted liver.

Nexavar® (sorafenib) is approved by the Food and Drug Administration (FDA) for treatment of patients with advanced kidney cancer and advanced unresectable (untreatable with surgery) liver cancer (hepatocelluar carcinoma).

It is not known whether sorafenib, the study medication, is effective in preventing cancer recurrence in high risk patients following liver transplantation. The purpose of this study is to determine if sorafenib is a safe and effective treatment option for preventing liver cancer in high risk patients following liver transplantation.

This study is being funded by Bayer Healthcare Pharmaceuticals.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 60 people will take part in this study at UCLA. About 356 people will participate in this study nationwide.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Before you begin the study:
The Study Doctor will ask you about your current health and your medical health history. The doctor will examine you and measure your height, weight, blood pressure and heart rate. You will also have a pregnancy test every three months while on study treatment if you are a female and are child-bearing potential. You will an electrocardiogram (ECG) (heart tracing) if not done within one year as part of your usual care, routine blood tests (about 3 teaspoons of blood), and Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) an imaging test of your chest, abdomen (stomach), and pelvis prior to start of treatment as per usual post-transplant care.

You will be randomly assigned (like flipping a coin) to one of the two treatment groups; one-half of the randomized patients will receive sorafenib; one-half of patients will receive a placebo (a pill that doesn't have any drugs or medicine). You will not know what group you are in until after the study is completed.

You will begin taking the study drug or placebo between 6-12 weeks after your liver transplant. You will continue taking the study drug or placebo for 24 months, then you will continue to be followed for an additional 2 years.

During the study:
Treatment Phase: Week 1, then every 2 weeks until week 8, then monthly until week 24, then every 3 months until Month 24

During the study, it is important to come to your visits as scheduled and take your medicines as your doctor has directed.

The tests that you will have during your time in the hospital and clinic that are related to the study are common to usual transplant care.

At every visit, your doctor or study staff will ask about:
• how you are feeling and about any side effects that you may have had
• if you have been in the hospital or have been seriously ill
• the medicines that you are taking in addition to your study medicine

• if you have missed any study medicine.

For every visit:

- You will have routine blood work done. About 3 teaspoons will be taken each time. It is important that this is fasting (that you do not eat or drink anything, except water, for at least 8 hours before the visit).
- It is very important that you bring your study medicine with you and keep all empty medicine bottles. The medicine will be counted to make sure that you have taken all the medicine as your doctor prescribed.
- A physical examination will be done at every visit.
- Your weight, blood pressure and pulse will be measured at every visit until the end of the study. In addition, your blood pressure will be monitored (either during your regular clinic visits or at home) two times a week for the 1st 6 weeks. These measurements should be recorded on the Home Blood Pressure Log provided to you.

The tests done at each visit are standard medical tests. A qualified nurse or clinician will be drawing the blood samples to ensure that the risk of drawing blood will be very small.

It is very important that you take the medicine given you just as the doctor tells you to. Do not miss any tablets. You will be taking the tablet(s) up to twice daily by mouth as directed by the study staff. For the 1st 4 weeks (28 days), you will be taking 1 tablet twice a day. If you are able to take this amount of study medication, then for the next month (day 29), you will be taking 1 tablet in the morning and two tablets in the evening. If you are able to take this amount of study medication, after two months (day 58), you will take 2 tablets twice a day until you have completed 24 months of treatment. Your dose of study medications will be adjusted if you have any side effects, such as skin problems, and or diarrhea. We will provide you with a dosing card so that you will know how much study drug to take at any time that your dose is adjusted. You must take the tablets without food (at least 1 hour before or 2 hours after a meal). Tell the study staff about any medications you are
taking during the study. This includes prescriptions drugs, over-the-counter medicines and vitamins. This is very important. Please tell your study doctor or study staff if you have any unusual symptoms.

During the Treatment Phase of the study, you will have an MRI or CT scan every 6 months. An MRI, also called magnetic resonance imaging, is a diagnostic procedure using a scanner to obtain detailed sectional images of the internal structure of the body. A CT scan, also called computerized tomography or just CT, combines a series of X-ray views taken from many different angles to produce cross-sectional images of the bones and soft tissues inside your body. These are routine post-transplant tests to check to see if your cancer has reoccurred.

Also during the Treatment Phase of the study, you may have a biopsy of your transplanted liver to check if liver cancer has recurred. A liver biopsy is done by inserting a needle into the transplanted liver and removing a tiny piece of liver for examination in the laboratory. Before the procedure, a local anesthetic (numbing shot) will be given at the needle site, and you could also be given medication to relax you.

Follow-up Phase: Month 30, 36, 42, & 48

You will have routine blood work done. About 3 teaspoons will be taken each time. It is important that this is fasting (that you do not eat or drink anything, except water, for at least 8 hours before the visit).

During the Follow-up Phase of the study, you will have an MRI or CT scan every 6 months. These are standard post-transplant tests to check to see if your cancer has recurred.

If you stop taking the study drug before the end of the treatment phase, we will ask that you complete an End of Treatment evaluation that will include:

- Physical examination
- Measurements of weight, blood pressure and pulse
- Routine blood work (about 3 teaspoons of blood will be taken)

HOW LONG WILL I BE IN THIS STUDY?

This study will last approximately 4 years after your liver transplant.

WHAT KINDS OF RISKS OR DISCOMFORTS COULD I EXPECT?

Known risks and discomforts:
All medications can produce some side effects. Your doctor will watch you very carefully for these side effects. Your doctor will ask you about side effects at every visit and may reduce or stop the amount of your study medication from time to time because of side effects.

Sorafenib
Sorafenib may interact with the anti-rejection medications that you take for your liver transplant**.** This unknown reaction of anti-rejection medications combined with treatment with sorafenib is the main risk of participating in this study**.** Through out the course of the study, you will be followed carefully for drug interactions.

The following adverse events have been reported in the 10,800 cancer patients who have taken sorafenib during the course of a research study.

LIKELY (Greater than 20%) Fatigue or tiredness, Hair loss, Rash/flaking or shedding of outer layer of skin, Inflammation or blistering of the skin on the palms of the hands or soles of the feet (this is painful), Loss of appetite, Diarrhea, Nausea, Weight loss, Abdominal pain, Low levels of a blood protein called albumin. A low albumin level is common in liver disease and other chronic illnesses. In general, there are no symptoms or ramifications unless the levels are very low and this can lead to fluid retention. Low blood phosphate level. Low phosphate levels have been associated with sorafenib. In general, there are no symptoms or ramifications unless the levels are very low and that can cause muscle weakness.

LESS LIKELY (Less than 20%) Allergic Reaction (Hypersensitivity reactions), Decrease in a red blood cell protein that carries oxygen in the blood (anemia), which may cause you to feel tired and short of breath, Decreased total number of white blood cells (leukopenia), which

may put you at risk for infection, Decreased number of a type of white blood cell, Low white blood cells can put you at risk for certain infections, Decreased number of blood cells that help to clot blood. Low platelets (the cells that clot blood) are commonly associated with liver disease. This can put you at risk for bleeding. High blood pressure, Fever, Difficulty sleeping of falling asleep, Dry skin, Itching, Constipation, Digestive symptoms (stomach acid, difficulty with swallowing and inflamed mouth), Painful inflammation and ulceration of the digestive tract, Vomiting, Bleeding in the digestive tract, Bleeding in the reproductive organs or urinary system (such as the bladder or kidney), Bleeding of the respiratory tract, Fever with a dangerously low white blood cell count, Infection with or without a low white blood cell count, Swelling of the arms and legs, Increased liver enzymes, which may cause inflammation to the cells in the liver, Abnormal liver or bone enzyme level, which may cause yellow skin (jaundice), fatigue, decreased appetite, nausea, itching or abdominal pain, Abnormal bone enzyme level, which may cause bone pain, increased bone fractures or bone deformities, Abnormal digestive enzyme level, which is not typically associated with any symptoms, High blood levels of a liver pigment indicative of abnormal liver function, Low blood calcium level (hypocalcemia), which may cause muscle cramps, High blood sugar (hyperglycemia), which may cause you to feel tired, increased thirst and urination, Low blood sugar (hypoglycemia), which may cause confusion, blurred vision, seizure and loss of consciousness, High blood potassium levels (hyperkalemia), which may cause irregular heartbeat, nausea, and slow pulse, Low blood potassium levels (hypokalemia), which may cause you to feel tired, an abnormal heart beat, constipation and muscle spasm, Low blood sodium level, Dizziness, Nerve damage causing numbness, tingling, or burning, Back pain, Chest pain, Leg pain, Headache, Joint pain, Muscle pain, Pain, Cough, Shortness of breath, Hoarseness, laryngitis, loss or change in voice, Kidney failure, Formation or presence of a blood clot inside a blood vessel, Depression, Erection problem (impotence), Tinnitus (ringing in the ears) & Excess serum proteins in the urine (proteinuria).

UNCOMMON (Less than 1%) Infection in the hair follicles, Reflux in the stomach and esophagus (heartburn), Severe skin condition with rash, skin peeling, and sores of the mucous membranes (Stevens-Johnson syndrome), Inflammation of the pancreas (pancreatitis), Gall bladder inflammation (cholecystitis, cholangitis), Chest pain (myocardial ischemia), Dehydration, reduced sodium (salt) level in the blood, Cancerous or precancerous lesions of the skin, Enlarged breasts in men, Persistent runny nose, Inflammation of the lung (interstitial lung disease like events) which may lead to breathing problems, Reduced or increased function of the thyroid gland, Yellow skin (jaundice) and increases in certain blood tests indicating temporary liver damage & Reduced blood clotting.

RARE BUT SERIOUS (Less than 3%) Congestive heart failure may be life threatening or fatal, Decreased blood supply to the heart, Heart attack, Decrease in the ability of the heart to pump blood, A hole somewhere in the intestinal tract from the esophagus to the anus, Bleeding into the brain or spinal cord, Syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings, High levels of protein passing from the blood to the urine (nephrotic sybdrome), Cellular death of bone components (osteonecrosis) & Interstitial lung disease-like events.

Drawing Blood

The risk of drawing blood may include pain, bruising, small blood clot formation and/or bleeding at the site of needle insertion for blood drawing. Very rarely an infection may occur at the site. You may also experience dizziness and/or fainting.

Liver Biopsies
There is some discomfort associated with the procedure. The discomfort should not last more than several hours. The risks include bleeding from the biopsy site, significant bleeding requiring a blood transfusion or surgery to control the bleeding (less than 1 of 1,000 patients), perforation (hole) of internal organs (less than 1 of 1,000 patients) and death (less than 1 of 10,000 patients).

Women and Men Who Are Able to Have Children
Sorafenib has been associated with an increased risk of birth defects. Therefore, if you are a woman, capable of becoming pregnant, you will not be enrolled in this clinical study until a negative pregnancy test result is obtained. You must agree to receive birth control counseling, and you must use effective birth control. You and your study doctor must discuss exactly what types of birth control are acceptable. Examples of adequate contraceptive methods include: barrier methods, Depo-Provera, Norplant, Ortho Evra (birth control patch), oral contraceptives, and complete abstinence. It is important for you and your doctor to agree upon two methods, and you must use the methods chosen. Unless you decide to avoid sexual intercourse completely, you must continue birth control, during the 2-year study, and for 30 days after taking the study medication. If you do become pregnant, you must notify your study doctor immediately. Breastfeeding should be discontinued during the study.

If sexually active, males must be able and willing to use adequate contraceptive methods throughout the study and for 30 days after the final dose of study medication. Barrier contraceptives (condoms or diaphragm) with spermicide, surgical sterilization, and complete abstinence are examples of effective methods.

Unknown risks and discomforts:
The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE ANY BENEFITS IF I PARTICIPATE?

Possible benefits to me:
The possible benefit of participating in this study is prevention of cancer recurrence after your liver transplant.

You will also receive the study drug free of charge.

Possible benefits to others or society:
This study will help the researchers learn more about whether sorafenib is helpful in preventing liver cancer recurrence after liver transplantation. Hopefully this information will help in the treatment of future patients who are at high risk of liver cancer recurrence.

WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?

If you decide not to take part in this study, or if you withdraw from this study before it is completed, the following alternative procedures or courses of treatment are available: you can receive standard of care. You do not have to participate in this research to receive care for your medical problem. You may choose to receive the standard care that is currently available for your liver transplant. Please ask your Study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether to participate in this research or receive the standard care that is currently available for your liver transplant. If you decide to participate in research now, and later change your mind, you may stop your participation in the research then and receive the alternative care.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The researchers may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk, if you do not follow instructions, if you miss scheduled visits, if you have an episode of a severe reaction, have liver cancer recurrence, become pregnant, or if your condition becomes worse. If you become ill during the research, you may have to drop out, even if you would like to continue. The researchers or the study sponsor might also decide to stop the study at any time.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

The researchers will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security.

Identifiable information about you will be replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data.
All research data and records will be maintained in a secure location at UCLA. Only authorized individuals will have access to it. Some research data and records will be stored electronically on a secure computer or with password protection.
The researchers intend to keep the research data and records until the research is published and/or presented.

The research team, authorized UCLA personnel, the study sponsors, Bayer Healthcare Pharmaceuticals, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

ARE THERE ANY COSTS FOR TAKING PART IN THIS STUDY?

The study sponsor will supply and pay for the cost of dispensing the study drug, pregnancy tests, and the extra related liver biopsies. However, you and your insurer will be billed for the costs of all other procedures, as these are considered standard of care.

You or your insurer will be billed for the costs of any standard medical care you receive during your participation in the study and you will be responsible for any associated co-payments and deductibles. There is a possibility that your medical insurance company may not cover these costs because you are in a research study. If this happens you might have unexpected expenses from being in this study, such as the costs associated with treating side effects. Financial counseling and itemized cost estimates are available upon request.

WILL I BE PAID FOR MY PARTICIPATION?

You will not be paid for your participation in this research study.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

The Research Team:

You may contact Drs. Busuttil, Kaldas, and/or [redacted] with any questions or concerns about the research or your participation in this study. You can also call the UCLA Page Operator at [redacted] to reach Drs. Busuttil, Kaldas, or [redacted] 24 hours a day, 7 days week.

UCLA Office of the Human Research Protection Program (OHRPP):

If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: [redacted]; by email: [redacted] or U.S. mail: UCLA OHRPP, [redacted]

Public Information about this Study:

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT HAPPENS IF I BELIEVE I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number(s) listed above.

If you are injured as a result of being in this study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California , or billed to you or your insurer just like other medical costs, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For more information about this, you may call the UCLA Office of the Human Research Protection Program at [redacted] or send an email to [redacted]

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from UCLA.
- If you decide to take part, you can leave the study at anytime.
- If you decide to stop being in this study you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
- If you decide not to take part, you can still get medical care from UCLA.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?
If you agree to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

SIGNATURE OF THE PARTICIPANT

_____
Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

_____ _____
Name of Person Obtaining Consent Contact Number

_____ _____
Signature of Person Obtaining Consent Date