Official title: A Phase II Trial of High Dose IL-2 and Stereotactic Ablative Body Radiation Therapy (SABR) for Patients with Metastatic Clear Cell Renal Cell Cancer (mRCC)

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The University of Texas Southwestern Medical Center
Parkland Health & Hospital System
Children's Medical Center
Retina Foundation of the Southwest
Texas Scottish Rite Hospital for Children
Texas Health Presbyterian Hospital Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	Phase II Trial of High Dose IL-2 and Stereotactic Ablative Body Radiation (SABR) for Patients with Metastatic Clear Cell Renal Cell Cancer (mRCC)
Funding Agency/Sponsor:	Department of Radiation Oncology at UTSW
Additional Funding:	Prometheus laboratories Inc. has provided a grant to provide a portion of the funds needed to perform the Study. Prometheus is not a sponsor of this Study.
Study Doctors:	Raquibul Hannan, MD, PhD 5801 Forest Park Road, 2nd Floor Dallas, Texas 75390-9183 (214) 645-8525

You may call these study doctors or research personnel at any time at 214-645-8525.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
This study is being done to find out the effects of receiving an FDA approved kidney cancer immunotherapy HD IL-2 treatment, in combination with FDA approved Stereotactic Ablative Body Radiation (SABR). Investigators wish to learn if the combination of these two treatments is more effective in keeping your cancer from getting worse than when any of these treatments is given alone.

Why is this considered research?
This is a research study because the combination of HD IL-2 and SABR is experimental in kidney cancer; it needs to be tested to determine if the combination is more beneficial than HD IL-2 or SABR alone. HD IL-2 is an FDA approved therapeutic cancer immunotherapy for kidney cancer. SABR is also an FDA approved therapeutic cancer treatment.

The following definitions may help you understand this study:

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you have metastatic kidney cancer.

Do I have to take part in this research study?
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?
About 33 people will take part in this study at UT Southwestern.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

Screening Procedures

To help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:

- Physical exam and medical history and current symptoms or problems
- Vital signs (blood pressure, pulse, temperature, respiratory rate, height, weight)
- You will be asked what medications you are currently taking
- Blood samples (about 7 tablespoons) will be drawn initially for routine tests (, cell blood count and; comprehensive chemistry which measures substances such as electrolytes)), for correlative immunological studies prior to HD IL-2, to check your immune response to SABR, and to check for HIV, Human T-lymphotropic virus Type I, and Hepatitis B and C. Whole blood samples (about 100 ml; 7 tablespoons) will be drawn at baseline, (other blood samples will be after second cycle of HD IL-2, 8 weeks, 6 months and one year after SABR administration. An additional 2 tablespoons of blood will be drawn one hour after SABR administration for the collection of proteins found in the blood.) Specimen may be shipped to companies or outside institutions to perform specialized assays, a non-extensive list of which is provided above. Specimen will be shipped de-identified.
- Pregnancy test (for females of child bearing age) will be done via blood or urine samples. The test will be performed using about 2 tsp. of blood or about 10 tsp. of urine and will be collected at the time of screening.
- Demographic information (age, sex, ethnic origin).
- Assessment of your ability to carry out activities of daily living
- A CT (Computed Tomography) scan using IV contrast of your chest, abdomen (stomach, intestines, liver, spleen and pancreas) and pelvis. A CT scan is a study using x-rays to look at one part of your body
- A bone scan to determine if the cancer has spread to the bones.
- Pulmonary function tests to determine lung function. They measure how well your lungs are working, by measuring how much air and how fast you can breathe in and out, and how much oxygen gets into your blood from your lungs, by breathing into a mouthpiece attached to a machine called a “spirometer”.
- A cardiac stress test with thallium to determine heart function. It is a nuclear imaging test that shows how well blood flows into the heart during exercise and at rest. A stress test is sometimes called an “exercise test” or a “treadmill test”. Prior to the test, a nurse or health care professional will insert an intravenous line (IV) usually on the inside of the elbow. A radioisotope or

radiopharmaceutical medication called thallium is injected through the IV. You will then lie down for 15 to 45 minutes while the medication settles in the heart. Then you will be asked to exercise or take a medicine (dobutamine) to make your heart pump faster. Your blood pressure and heart rhythm are monitored while you exercise. Once your heart is working at full capacity, you will be given another radiopharmaceutical injection and wait for 15 to 45 minutes. Images of your heart will be taken for your doctor to analyze the strength of your blood flow to your heart. A test called an ECG (electrocardiogram) is done during the stress test. For the ECG, patches (called "electrodes") are stuck to a person's chest. Wires run from the patches to the ECG machine to measure the electrical activity in the heart. You will also have your blood pressure checked during the stress test.

- A CT-guided biopsy of tumor will be performed. Biopsy is the process of taking a sample of tissue from the body for analysis. CT will be used in biopsies to provide images that help guide the tools or equipment necessary to perform the biopsy to the appropriate area of the body. If you have had a recent biopsy (within three months) and tissue blocks are available, you will not need another biopsy prior to the study enrollment. Biopsies will be processed as routine diagnostic specimens to confirm your metastatic cancer by Pathology for the purpose of diagnosis and Immumo-histochemistry (IHC) (a laboratory test that uses antibodies to test for certain antigens). Additional samples will be stored at Dr. Hannan's research laboratory for research purposes. If you have participated previously in protocols [such as the Urology Tissue Repository Protocol (STU 032011-187)] or procedures and the tissue confirming kidney cancer diagnosis is in storage and available in UTSW Medical Center or an outside institution, the study team may request a tissue sample.

  An additional <u>optional</u> biopsy will be performed 8 weeks after your last SABR treatment.

- You will be asked to fill out a Quality of Life Questionnaire (QoL)

<u>Pre-treatment:</u> As part of the pre-treatment planning session, you may undergo several procedures to help make the treatment more accurate.

Simulation: Simulation is the planning stage of radiation therapy. During simulation, you will be asked to lie still on a table and a body mold will be made. This body mold will keep you in position during the radiation therapy treatment. During that visit, a CT scan with contrast will be obtained to capture information about the tumors. This 3-D image allows the physicians to see all sides of the tumor and can plan for the radiation beams to be exactly focused on the tumor. Once the CT scans are obtained, the physicians, medical physicists and the radiation dosing specialist utilize the computerized planning system to create the treatment plan.

Treatment

If you decide to participate in this study you will undergo Stereotactic Ablative Body Radiation (SABR) treatment for one week. If SABR needs to be used for multiple sites, an additional five days is allowed for the completion of the treatment. Your first cycle of HD IL-2 treatment will be started within 72-84 hours of your last SABR treatment. A typical radiation treatment lasts about 30-90 minutes. The body mold will be used daily with your treatment to keep you still and varies with the location treated. Treatment will be given on an outpatient basis. This means that you will not have to stay in the hospital overnight. SABR is a non-invasive treatment in which high doses of radiation beams are delivered to a tumor in a concentrated, precise manner. Because the beams enter the body from different angles and intersect at the tumor, the surrounding healthy cells are often spared.

For the purpose of HD IL-2 treatment, you will need to be admitted to the ICU of the hospital for about five days for close observation. Prior to receiving HD IL-2 treatment you will have a central venous catheter placed in your body. This procedure is usually done with a local anesthetic which will induce a temporary loss of sensation or pain in that area. This central line will allow the medical drug to be delivered to the great veins near the heart so they are dispersed quickly throughout the body. You will then receive an intravenous bolus which means that the medication will be delivered through the veins. Each dose of HD IL-2 is given over a fifteen minute time period via your central line.

Plan to have someone drive you home once you are finished. Most people feel fatigued after the procedure. To help minimize a possible reaction to the infusion such as chills and fever, your doctor may decide to give you Tylenol, anti-nausea, anti-acid (to decrease acid secretion in your stomach) and intravenous fluid with potassium supplementation among other treatments to prepare your body for the infusion. For the purpose of managing the side effects of HD IL-2 infusion, you may receive various treatments during your hospital stay including, but not limited to, antibiotics, anti-fever medications, anti-nausea, anti-acid, blood pressure medications, intravenous fluids and electrolyte supplements. Upon completion of the treatment, you may also need to take some of these medications at home for a period of time.

You will get a 7 day break between your first cycle HD IL-2 and your second cycle of HD IL-2, which together is called one course of HD IL-2. At the discretion of your physician, you may receive up to three courses of HD IL-2.

Time and Events Table

	Pre-study	Cycle 1 , Day15 (+/- 5)	Cycle2, Day30 (+/- 14)	Cycle2, Day37 (+/- 14)	Months 1-8: q8 Weeks	Months 8-18: q12 Weeks	Months 18-120: q3-6 months
Assessment	X				X	X	X
Informed Consent	X						
Vital Signs	X	X	X	X	X	X	X
History and PE	X				X	X	X
Performance Status	X				X	X	X
Toxicity (include DLT) Evaluations	X				X	X	X
Bone Scan	X				X*	X*	X
CT Chest, Abd, pelvis w/ Contrast	X				X	X	X
Biopsy of metastatic lesion	X^				X@		
CBC with diff	X	X[1]	X[1]	X[1]	X	X	X
Basic Chemistry	X	X[1]	X[1]	X[1]	X	X	X
Comprehensive chemistry (see 5.1.11)	X			X	X&		
Blood collection for Immune Assays	X			X	X#	X#	X#
QOL Questionnaires	X			X%	X%	X%	X%
Cardiac Stress Test	X						
PFT	X						

* Bone scan performed every 8 weeks only if bone lesions present in baseline bone scan.
@ optional
# Immunologic blood collection is needed at baseline, post SABR, post HD IL-2, at 8 week, 6 months and 1 year
& Comprehensive chemistry will be done once a year, after this point.
% Cost and Convenience Questionnaire will only be administered at the first follow up. All other QoL surveys will take place every other follow-up.
1 Additional procedures, ICU admission, and lab requirements may apply in association with IL-2 administration, as detailed in appendix C.
^ if previous biopsy of metastatic site within six months with adequate review of slides is not available. If the patient participated in protocols [such as the Urology Tissue Repository Protocol (STU 032011-187)] or procedures where tissue confirming kidney cancer diagnosis was collected and the biopsy in storage is still available, the study team may request a tissue sample.

Evaluations during the research

• Procedures that are part of regular cancer care and may be done even if you do not join the study:

Procedure	Schedule
History and physical exam	Prior to study entry, prior to each treatment cycle and 8 weeks after study entry.
Vital Signs	Prior to study entry, and every time you are seen in the clinic.
Assessment of your ability to carry out activities of daily living	Prior to study entry and 8 weeks after study entry.
CT Scan of chest, abdomen, and pelvis, Tumor Measurements, Bone Scan	Prior to study entry and 8 weeks after study entry if necessary.
Blood samples for routine tests (Hematology and chemistry)	Prior to study entry and at every clinical visit after study entry.
PFT and cardiac stress test	Prior to study entry

• Procedures that are related to this study:

Procedure	Schedule
CT Simulation for radiation treatment planning	One week prior to SABR
Stereotactic Ablative Body Radiation	Total of 1 or 3 treatments
Assessment of your ability to carry out activities of daily living	Initially and every 8-12 weeks for two years
CT Scan of chest, abdomen, and pelvis, Tumor, Measurements, Bone Scan	Prior to entry study and every 8-12 weeks after study entry.
Blood samples (about 4 tablespoons) will be drawn for routine tests (Hematology and chemistry)	Every time you are seen in the clinic.
Side Effects evaluation	Prior to study entry, every 12 weeks for 2 years after you complete radiation, and every 6 months thereafter
Blood samples to check your immune response to SABR (about 7 tablespoons)	Prior to study entry, last day of HD IL-2 on the second cycle, on week 8, 6

	months and at one year.
Blood sample (2 table spoons) to check for serum cytokines, proteins used by the immune system.	1hours after first SABR treatment
Quality of Life questionnaires	Prior to study entry, last day of HD IL-2, week 8, then every 4 months
Biopsies	At study entry and optional biopsy at 8 weeks after last SABR

You may have magnetic resonance imaging (MRI) of your chest, abdomen or pelvis. For this procedure, you will lie quietly inside a large, doughnut-shaped magnet for about 30 minutes. You will not need an MRI of the head.

If participated previously in protocols [such as the Urology Tissue Repository Protocol (STU 032011-187)] or procedures where tissue confirming kidney cancer diagnosis was collected:
This tissue is being obtained for research purposes and will not affect your treatment. It may help doctors in the future direct therapy for individuals like you. Your participation in this part of the study is voluntary and will not affect your overall participation in the rest of the study. If your biopsy in storage is still available at UTSW Medical Center or an outside institution, the study team may request a tissue sample.

Yes _____initials No _____initials N/A_____initials

Consent for optional tumor biopsy 8 weeks after SABR:
This tissue is being obtained for research purposes and will not affect your treatment. It may help doctors in the future direct therapy for individuals like you. Your participation in this part of the study is voluntary and will not affect your overall participation in the rest of the study. The entire procedure will be explained by your doctor and you may still refuse at any time. A CT-guided biopsy of tumor will be performed. Biopsy is the process of taking a sample of tissue from the body for analysis. CT will be used in biopsies to provide images that help guide the tools or equipment necessary to perform the biopsy to the appropriate area of the body. (A “no” answer will not disqualify you from this research.)

Yes _____initials No _____initials

How long can I expect to be in this study?
It is estimated that you will complete both SABR and HD IL-2 between 4-7 weeks from your first SABR treatment. If you have unacceptable side effects or illness that prevents you from continuing on the study you could be removed from the study sooner.

You will be asked to participate in the follow-up phase of the study for about ten years after you complete or stop receiving HD IL-2 and SABR. You will be followed every 8 weeks until eight months. After eight months, you will be followed for every 12 weeks for a total of 2 years, and then every sixteen weeks for another three years and every six months for the next five years. After ten years, it will be up to your doctor whether or not they feel more follow-up is needed. Each follow up will consist of a combination the following:

- Physical exam
- Vital signs
- About 2 tablespoons of Blood samples will be drawn for routine tests (Hematology and chemistry), ,
- Additional 7 tablespoons blood will be collected to check your immune response to SABR during the first year.
- A bone scan and/or a CT scan using IV contrast of your chest, abdomen and pelvis
- You will be asked to fill out a Quality of Life Questionnaire

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

Procedures for Storing of Extra or Left Over Samples
Extra or left over samples will be retained at the department of pathology and at the lab of Dr. Hannan (NC7. 208). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by you as a participant, best efforts will be made to stop any additional studies and to destroy the specimens. Dr. Hannan will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UTSW. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. The following information obtained from your medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available

What are the risks of the study?
Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider.

Risks Associated with HD IL-2
HD IL-2 may cause some, all or none of the side-effects listed below.
In previous controlled studies, 71% of patients in the HD IL-2 group developed an acute infusion reaction. Most commonly reported toxicity:

Very likely (>10%)

- Nausea
- Vomiting
- Diarrhea
- General tiredness
- Itchy and peeling skin
- Difficulty sleeping
- Difficulty breathing
- Flu like symptoms such as fever, chills and muscle aches
- Decrease in appetite
- Low blood pressure and rapid heart beat
- Weight gain, Water retention
- Changes in mental status such as confusion
- Low urine output

Less likely (1-10%)

- Irregular heart beats
- Heart Attack
- Bleeding
- Infection
- Enlarged abdomen due to water retention
- Difficulty breathing
- Severe confusion
- Little to no urine production
- Stuffy nose, runny nose, nose drainage

Rare, but serious (<1%)

- Stroke
- Breathing problems, ceasing to breath
- Fainting
- Seizure
- Blindness (temporary or permanent)
- Severe Depression

- Hemorrhage (brain, intestines and organs in abdominal area)
- Nerve Damage
- Diabetes
- Death
- Liver failure
- Ulcers in stomach or intestine
- Heart Problems
- Lung Problems and thus problems breathing
- Failure of blood flow to the brain
- Kidney Failure
- Infection at the injection site
- Infection at other sites
- Bleeding
- Extreme body temperature changes (hypothermia, hyperthermia)
- Severe increase in blood pressure
- Confusion/Disorientation
- Brain swelling, brain lesions
- Asthma

Risks Associated with Stereotactic Ablative Body Radiation

Stereotactic Ablative Body Radiation cause some, all or none of the side-effects listed below, depending on where in your body you will receive radiation.

Very Likely (>10%)

- Tanning or redness of skin in treatment area
- Rash, itching or peeling of skin
- Temporary hair loss in the treatment area
- Temporary fatigue, nausea or diarrhea
- Infection
- Indigestion
- Abdominal cramps
- Abdominal bleeding
- Jaundice (the yellowish staining of the skin and whites of the eyes)
- Fluid collection in the abdomen
- Irritation of the pancreas
- Elevated liver enzyme blood levels
- Fever, chills
- Damage to lung tissue
- Damage to digestive organs, kidneys and spleen
- Erection problems (may not be reversible)

- Rectal irritation with frequent urge to have a bowel movement
- Bladder irritation with frequent urge to urinate
- Bowel Movements with Mucous
- Burning on urination
- Injury to urethra which may cause narrowing (may need surgical correction)

Less Likely (< 3%)

- Incontinence
- Fracture of bone

Less Likely, but Serious (<3%)

- Injury to the area that is receiving radiation
- Rectal bleeding, intestinal or urinary obstruction, sterility, and ejaculatory dysfunction (may not be reversible)
- Pain that may not be reversible
- Bowel blockage
- Vomiting up blood
- Dysfunction of your kidneys
- Liver failure
- Paralysis of limbs

Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious, long-lasting, or permanent. It is also possible that your cancer may not respond to radiation therapy.

The radiation therapy used in this research is the standard radiation therapy for your health problem; therefore, the risk of harm to your body is the same. Your radiation doctor will discuss the known risks of radiation therapy with you and ask you to sign a separate specific treatment site consent form.

Risks Associated with MRI

Some or all of the following information may be appropriate for your study.

There are no known risks from exposure to magnetic fields. You may experience nervousness and/or anxiety due to the loud banging made by the machine while it is taking pictures and from confinement in a tight space (claustrophobia). If you become anxious, you can stop the procedure at any time.

You may also experience some discomfort and fatigue from lying still during imaging.

If you have any metal clips or plates in your body, you should tell the investigator. MRI may not be appropriate if you are pregnant or are trying to become pregnant. MRI may not be appropriate if you have permanent eyeliner or eyebrows or any pieces of metal in your body, such as the following:

- heart pacemaker, heart valve replacement, or aortic clips
- metal fragments in your eyes, skin, or elsewhere in your body
- brain clips or pieces of metal used in aneurysm surgery or intercranial bypass
- venous umbrella
- pieces of metal in the body resulting from work as a sheet-metal worker or welder
- clips placed in an internal organ
- prosthetic devices, such as middle ear, eye, joint, or penile implants
- joint replacement.
- hearing aid that cannot be removed
- neurostimulator
- insulin pump
- stainless steel IUD (intrauterine device). Copper IUD's are acceptable.
- shunts or stents
- metal mesh or coil implants
- metal plate, pin, screws, or wires, or any other metal implant

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called Gadolinium (dye solution used to highlight organs or tissues during imaging).The injection of Gadolinium may cause discomfort like headache, nausea, strange taste, or coldness at site of injection. These symptoms occur in less than 1 out of 20 patients receiving Gadolinium and go away quickly. There is a small risk of a severe allergic reaction that can cause breathing difficulties and/or low blood pressure, these symptoms are extremely rare (approximately 1 in 10,000 to 1 in 100,000 administrations). In the unlikely event you experience these symptoms, a physician and nursing staff will be available to evaluate and, if necessary, provide treatment.

People with severe kidney failure who receive Gadolinium (dye used to highlight organs or tissues during imaging) are at risk of developing a disorder called Nephrogenic Systemic Fibrosis (NSF). This disease can cause wide spread tissue scarring or hardening (fibrosis). In rare cases NSF can lead to lung and heart problems and cause death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF is 1-5%. We may perform a blood test 30 days before your MRI to check your how well your kidneys are working before you receive the Gadolinium. This test may be repeated closer to your MRI appointment if your medical condition has changed. If your kidneys are working at levels known to be at risk for NSF, you will not receive Gadolinium. You will not receive Gadolinium for research purposes if you have either sickle cell disease or a low red blood count (anemia) since it may put you at risk of developing Hemolysis (breakdown of blood cells).

Risks Associated with Local Anesthesia

Very Likely (>10%)

- Pain at injection site

Likely (3-10%)

- None

Less Likely (<3%)

- Large swellings that look like hives on the skin in the mouth or in the throat
- Severe headache
- Blurred or double vision
- Dizziness or lightheadedness
- Drowsiness
- Confusion
- Anxiety, excitement, nervousness or restlessness
- Seizures
- Feeling hot, cold or numb
- Ringing or buzzing in the ears
- Shivering or trembling
- Sweating
- Pale skin
- Slow or irregular heartbeat
- Breathing problems
- Unusual weakness or tiredness

Risk Associated with Biopsies

- Pain
- Swelling
- Bleeding
- Infection

Psychological Stress

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality.

Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or
(2) a condom used with a spermicide (a substance that kills sperm).

Females: If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study. If you take part in this study and you are sexually active, you and any person that you have sex with must use medically-acceptable birth control (contraceptives) during the study.

Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or "tubes tied"),
(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera,
Depo-Lupron, Implanon),
(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or
(4) an intrauterine device (IUD).

If you do become pregnant during this study, you must tell the researchers immediately. Radiation exposure to a woman's reproductive organs may harm an embryo or fetus. Also, if radioactive materials are used for certain types of scans, harm may come to an embryo, fetus, or an infant who is breast feeding. Pregnancy tests performed during the early stages of pregnancy do not always reveal pregnancy. Therefore, radiation exposure that includes the reproductive organs will be limited to the first ten days after a woman who can become pregnant has begun her most recent menstrual period. This is standard policy in clinics and hospitals within UT Southwestern. This policy applies unless there is an important medical reason requiring radiation outside this time frame

Risks of Radiation – Diagnostic Test

The radiation dose that you will get from diagnostic tests is medically indicated for your condition and it is the same that you would get if you were not involved in this research study.

Risks Associated with Blood Drawing
Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

You will have about 2 tablespoons of blood collected because you are in this research study.

Risks Associated with Pulmonary Function Tests
Pulmonary function tests are usually safe for most people. However, because the test may require you to inhale and exhale rapidly, you may experience coughing, light-headedness or dizziness. It can also cause a feeling of pressure in the chest, belly or head.

Risks Associated with Thallium Cardiac Stress Test
Most people tolerate the test very well. If used, you may feel a sting as the medication that simulates exercise (Dobutamine) is injected, followed by a warm feeling. Some patients may experience headache, nausea, and a racing heart.
Complications from the test are rare, but may include:

- arrhythmias (irregular heart beat)
- increased angina (pain from poor blood flow in the heart)
- difficulty breathing
- asthma-like symptoms
- large swings in blood pressure
- skin rashes
- shortness of breath
- chest discomfort
- dizziness
- heart palpitations (an irregular heartbeat)

The electrocardiogram performed during the stress test has very few downsides; some people get a mild rash where the patches were placed. Because the stress test involves exercising and the heart pumps fast, you may experience symptoms such as an abnormal heartbeat, trouble breathing or feeling dizzy or faint. The medicines used during a stress test can also cause side effects, including headaches, dizziness or nausea.

There are no known adverse effects from diagnostic ultrasound at clinical imaging frequencies, so the addition of echocardiographic imaging to stress testing (either exercise or pharmacologic) does not alter the underlying risk of the stress test.

There are a number of minor noncardiac side effects including nausea, anxiety, headache, tremor, and urinary urgency, which can lead to test termination in very few cases.

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?

Procedures will be used to minimize any potential risks or discomfort. Staff will receive necessary training. You will be monitored for side effects. You will be withdrawn from the study should you experience harmful side effects. Referrals for treatment, counseling or other necessary follow-up will be provided.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or illnesses while you are on the study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?

If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?
If you agree to take part in this study, there may not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research. However, we hope that a combination treatment of SABR and HD IL-2 may result in a better cancer control than administering just HD IL-2.

We hope the information learned from this study will benefit others with cancer in the future. Information gained from this research could lead to better treatment options for people with cancer.

What options are available if I decide not to take part in this research study?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- Getting treatment or care for your cancer without being in a study.
  - Chemotherapy
  - HD IL-2 T alone
- No treatment except medications to make you feel better (However, the disease could continue to spread).
- Taking part in another study.

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?
No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Will my insurance provider or I be charged for the costs of any part of this research study?
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.

HD IL-2 is not being provided to you free of charge. Either you, or your insurance provider, will be responsible for the cost of HD IL-2. Since HD IL-2 is FDA approved and a standard of care, it is covered by most health insurance. If SABR is also a

standard of care for your condition, it will also be billed in a similar manner.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or Prometheus Laboratories.

You retain your legal rights during your participation in this research.

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. He is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?
Medical information collected during this study and the results of any test or procedure done may be included in your medical record and this information may be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records, adverse event analysis and reporting for research, quality assurance, and data analysis include:

- Department of Radiation Oncology at UTSW (sponsor) and Data Safety Monitoring Board
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board.
- Simmons Comprehensive Cancer Center Data Safety Monitoring Board
- Prometheus Laboratories

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.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Are there procedures I should follow after stopping participation in this research?
Yes. If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Return any unused study materials, including empty containers.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Whom do I call if I have questions or problems?
For questions about the study, contact Raquibul Hannan, MD, PhD at 214-645-8525 at any time.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
- You understand that a copy of this signed consent document, information about this study and the results of any test or procedure done may be included in your medical record and this information may be available to health care providers and authorized persons including your insurance company.

_____		
Name of Participant (Printed)		
_____	_____	_____ AM / PM
Signature of Participant	Date	Time
_____		
Name of Person Obtaining Consent (Printed)		
_____	_____	_____ AM / PM
Signature of Person Obtaining Consent	Date	Time

Interpreter Statement:

I have interpreted this consent form into a language understandable to the participant and the participant has agreed to participate as indicated by their signature on the associated short form.

_____		
Name of Interpreter (Printed)		
_____	_____	_____ AM / PM
Signature of Interpreter	Date	Time