INTERNATIONAL EVALUATION OF RADIOTHERAPY TECHNOLOGY EFFECTIVENESS IN CERVICAL CANCER (INTERTECC):

PHASE II/III CLINICAL TRIAL OF INTENSITY MODULATED RADIATION THERAPY FOR CERVICAL CANCER

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University of California, San Diego
Consent to Act as a Research Subject

PHASE II/III CLINICAL TRIAL OF INTENSITY MODULATED RADIATION THERAPY FOR CERVICAL CANCER

Protocol #110808

Dr. Loren Mell and his colleagues are conducting a research study to find out more about a new radiation technique called "image-guided bone marrow-sparing intensity modulated radiation therapy (IG-BMS-IMRT)." You are being asked to take part because you have a cervical cancer.

Your participation in this research study is voluntary. The purpose of this Informed Consent Form is to inform you about the nature of this research study so that you may make an informed decision as to whether you would like to participate. If you have any questions, please ask your study doctor or coordinator to explain any words or information that you do not understand.

PURPOSE

The purpose of this study is to find out whether patients with cervical cancers treated with IG-BMS-IMRT have fewer side effects and better quality of life with equal cancer control compared to standard radiation techniques. This technique uses the imaging technique PET/CT to get a better picture of the area needing radiation therapy. Researchers believe this will help the "aim" of the radiation beam to reduce radiation dose to the normal pelvic organs near your tumor.

With standard radiation techniques, normal pelvic organs near your tumor receive radiation dose, which leads to side effects. IG-BMS-IMRT is a new radiation technique that can reduce radiation dose to these organs and may reduce side effects.

Participation in this study is entirely voluntary. 415 patients will take part in this multi-center international study. Approximately 75 patients will be enrolled at UC San Diego.

DURATION OF THE STUDY

The expected duration of this study is approximately 5 years.

IMAGING STUDIES

All imaging studies will be performed using standard techniques that will be performed by authorized personnel trained and licensed to perform the study or studies in question.

STANDARD TREATMENT AND PROCEDURES

Standard treatment for your disease consists of chemotherapy and radiation therapy. The chemotherapy in this study will be exactly the same as you will get if you do not participate in the study. The radiation therapy technique (IG-BMS-IMRT) will be the only difference in your treatment. IG-BMS-IMRT is not considered standard. As part of standard care, the following procedures may be required, whether or not you choose to participate in this study:

Pretreatment Evaluations

After signing this consent form you will have to undergo the following tests and procedures to determine if you are a good candidate to participate further in the study. Depending on when you last had these tests and procedures performed, some of them may not need to be repeated.

- Medical and surgical history review (including medications that you are taking or have taken in the past.
- Complete physical examination, including height, weight & vital signs (blood pressure, heart rate, temperature, breathing rate).
- Blood samples will be taken for the following lab tests:
  - Hematology or CBC (Complete Blood Count), which includes: white blood cell count, red blood cell count, platelet count, hemoglobin (oxygen-carrying pigment in red blood cells), hematocrit (measures the amount of space red blood cells take up in the blood). This is to aid in diagnosing anemia (low red blood cell count which can result in fatigue), certain cancers of the blood, and to monitor blood loss and infection.
  - Blood chemistry (which measures the levels of a number of chemical substances that are released from various tissues in the body to evaluate the function of the liver and kidneys)
  - HIV positive patients may still be eligible for this study if they have a $CD4^+$ T cell count greater than 200 per µL of blood and greater than 14 percent of all lymphocytes. A sample of your cervical or vaginal cells will be collected in a manner similar to a pap smear and the cells will be assessed under a microscope.
- Chest x-ray, chest CT, or PET/CT
- Pelvic CT scan or MRI
- CT or PET/CT simulation. This is when your study doctor will decide the best way to deliver the dose of radiation and limit the exposure of your vital organs.
- Pelvic MRI and/or PET/CT for radiation planning
- Collect demographic information about you, like your age, ethnicity, living situation, and health history information.

- Evaluation of side effects.
- Evaluation for Quality of Life.

Treatment Procedures

You will receive radiation therapy daily for 5 to 5½ weeks.
You will also receive weekly chemotherapy.

In addition, once a week you will have the following evaluations/tests done:

- Physical examination and vital signs
- Collection of blood samples for laboratory testing to check for normal organ function and to find out your disease status
- Review of any side effects

Post Treatment Procedures

At 1 week, 2 weeks and after your last dose of external radiation you will return for the following procedures:

- Collection of blood samples for laboratory testing to check for normal organ function and to find out your disease status
- Review of any side effects

At 1 month after your last study treatment you will return for the following procedures:

- Medical and surgical history review (including medications that you are taking or have taken in the past.
- Complete physical examination, including height, weight & vital signs (blood pressure, heart rate, temperature, breathing rate).
- Collection of blood samples for laboratory testing to check for normal organ function and to find out your disease status
- Review of any side effects
- Evaluation of the outcome of your treatment.
- Evaluation for Quality of Life.

At 3-4 months after your last study treatment you will return for the following procedure:

- PET/CT

At 6, 12, 24, and 36 months after your last study treatment you will return for the following procedures:

- Physical examination and vital signs

- Chest x-ray, chest CT, or PET/CT

- Pelvic CT scan or MRI to evaluate response to treatment and disease status
- Review of any side effects
- Evaluation for Outcomes
- Evaluation for Quality of Life.

Description of Procedures:

CT scan: The CT scanner is a free-standing machine with a large hole in the center. You will be asked to lie on your back with your arms raised above your head on a narrow table that slides into the hole. Patients who have difficulty with enclosed spaces such as those found with some MRI scanners do not usually have a problem with this type of test. A dye may be injected into a peripheral vein to better evaluate certain diseases and organs. The radiologist will decide if this is necessary. Tell the technician or radiologist if you have any allergies or have had difficulty with prior CT scans. It is very important that you remain still throughout the exam and hold your breath when asked. This will allow for better images. The actual scan time is usually about two minutes, although the entire procedure usually takes much longer.

MRI: Magnetic Resonance Imaging (MRI) may be done to measure your tumor. MRI uses magnetism instead of x-rays to build up a picture of the inside of the body. The scan is completely painless, but can be rather noisy and you have to lie very still inside the center of a large, doughnut-shaped magnet for approximately 30-60 minutes to get a good picture. If you have a pacemaker or other metal implants, the staff needs to know as the scan uses magnets.

Chest X-ray: This test is performed by an x-ray technician. You will be asked to stand in front of the machine and must hold your breath when the x-ray is taken.

Positron Emission Tomography (PET scan): You will be taken into a special injection room, where the radioactive substance is administered as an intravenous injection (although in some cases, it will be given through an existing intravenous line or inhaled as a gas). It will then take approximately 30 to 90 minutes for the substance to travel through your body and accumulate in the tissue under study. During this time, you will be asked to rest quietly and avoid significant movement or talking. After that time, scanning begins. This may take 30 to 45 minutes.

Hemogram or CBC (Complete Blood Count), which includes: white blood cell count, red blood cell count, platelet count, hemoglobin (oxygen-carrying pigment in red blood cells), hematocrit (measures the amount of space red blood cells take up in the blood). This is to aid in diagnosing anemia (low red blood cell count which can result in fatigue), certain cancers of the blood, and to monitor blood loss and infection.

Blood chemistry: measures the levels of a number of chemical substances that are released from various tissues in the body to evaluate the function of the liver and kidneys.

HIV test: in order to make sure that the study procedures are appropriate for you (HIV testing may require a separate consent form for you to sign. This form will be provided by the Study Doctor.)

RISKS OF PARTICIPATION

Research Procedures

Participation in this study may involve some added risks or discomforts, as explained below. There may also be other side effects that we cannot predict. Many side effects go away shortly, but in some cases, side effects may be serious, long-lasting, and may even cause death.

Side effects from IG-BMS-IMRT, in addition to those of standard radiation therapy (listed above), may include:

- Second cancers (rare, less than 1%)

Standard treatment for your disease may involve risks and discomforts. You will be at risk for the side effects listed below, whether or not you choose to participate in this study. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Medicines and other treatments can be given to make the side effects less serious and uncomfortable. Many side effects go away shortly, but in some cases, side effects may be serious, long-lasting, and may even cause death.

Risks and side effects related to radiation therapy include:

Likely (more than 10%)

- Redness and skin irritation in the treatment area that may result in bleeding and/or infection, which may require hospitalization
- Loss of pubic hair in the treated area, usually temporary
- Tiredness
- Nausea and/or vomiting
- Sterility (inability to bear children) in fertile women
- Sterility (inability to produce children) in men

Less Likely (3-9%)

- Diarrhea
- Sores and bleeding from the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Narrowing and dryness of the vagina (birth canal) and genital area with painful or difficult intercourse and possibly bleeding

- Development of extra tissue (fibrosis) in the anal canal, which may result in decreased function
- Long-term dryness of the skin
- Inability to have or keep an erection (impotency)
- Hip or pelvic or sacral fracture
- Build up of fluid in ankles, feet, and/or legs

Rare, but serious (less than 2%)

- Narrowing or blockage of the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Blockage of the urinary tubes
- Development of an abnormal path or connection between organs (fistulae)
- Skin damage (tissue death), which may result in surgery
- Narrowing of or persistent bleeding in the vagina (birth canal), which may result in surgery

Risks and side effects related to chemotherapy include:

- Kidney toxicity
- Ringing in the ears and/or hearing loss
- Bone marrow suppression
- Nausea
- Vomiting
- Diarrhea
- Low appetite
- Nerve injury
- Muscle cramps
- Loss of taste
- Seizures
- Blurry vision
- Altered color perception
- Allergic reactions (swelling, wheezing, increased heart rate, low blood pressure)
- Liver toxicity
- Other infrequent toxicities including heart toxicity, hiccups, rash, hair loss, malaise, and low energy, skin toxicity, or muscle toxicity.

Risk of Testing for HIV: As part of your treatment, you may be tested for HIV. These tests are necessary to make sure that the treatment is appropriate for you. Testing for HIV may result in a diagnosis of infection with this virus. You will be informed of the results of these tests; if you do not wish to know the results, you should let your doctor know. In the event that you are diagnosed with HIV, your doctor will give you the results in a face-to-face

discussion (not by telephone or mail), counseling will be offered to you, and the results will be entered in your medical record and provided to the California State Board of Health. In the event that you are diagnosed with HIV, you may be referred to a doctor who specializes in these illnesses. The diagnosis of HIV may result in earlier treatment and/or prevention of many complications from the illnesses. Efforts will be made to keep your personal information confidential. Awareness of a diagnosis of these illnesses may have serious personal or social consequences. Some of these consequences include possible difficulty obtaining health insurance or employment, and difficulty traveling to some foreign countries.

Allergic Reactions: There is the chance that your treatment could cause an allergic reaction, which may include difficulty breathing, rash, flushing, weakness, dizziness, lightheadedness, and swelling.

Intravenous (IV) Injection Side Effects: If the drug leaks from the vein where the needle was inserted, it may cause skin irritation at the needle site. Injections into your vein have a slight risk of pain, bruising, bleeding, infection, and rarely, fainting and/or nerve damage.

Risks of blood draws: There is a risk of discomfort or pain, bleeding, swelling and a small arm bruise and swelling when blood is drawn. Rarely, a clot or infection may occur at the site of the blood draw. Some people also become faint, dizzy, or light-headed during or immediately after the blood draw.

Reproductive Risks: You should not become pregnant while on this study because the drugs in this study can affect a fetus and cause serious birth defects. Women should not breastfeed a baby while on this study. The treatments used for your disease will make you unable to have children in the future. It is important you understand that if you are capable of child-bearing then you need to use birth control while on this study. If you are female and capable of child-bearing, a pregnancy test will be done before the study begins in order to be as sure as possible that you are not pregnant. Your treatment requires that you use contraception methods (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study. Ask about counseling and more information about preventing pregnancy.

Risks from X-rays and/or Scans: As part of your treatment, you will have imaging scans. These tests are necessary to evaluate, plan the treatment for, and monitor your disease. As a result of participating in this study, you will be exposed to a significant amount of radiation from diagnostic tests (approximately 175 mSv). This amount is more than you would receive from a year of natural exposure, which is approximately 1.6 mSv. This exposure may slightly increase your chances of developing cancer in the future. If you are especially concerned with radiation exposure or you have had a lot of x-rays already, you should discuss this with your doctor. Note that exposure you will receive from diagnostic procedures, however, is much less than the exposure you will receive from treatment, which is more than 45000 mSv.

Risks of MRI Scans: As part of your treatment, Magnetic Resonance Imaging (MRI) may be done. The imager makes a loud, banging noise while it is taking pictures. You will be given a set of ear plugs to help with the noise. You may experience feelings of claustrophobia or anxiety. You may also experience some discomfort and tiredness from lying still in a confined space during the imaging. There are no known effects from exposure to magnetic fields (MRI). However, some patients undergoing this procedure become anxious. If this happens to you, you can stop the procedure at any time. If you have metal clips or plates in your body or a pacemaker, you should tell your doctor about it. MRI may not be appropriate under some of the following conditions: a cardiac pacemaker; metal fragments in eyes, skin, or body; heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; aneurysm surgery; intercranial bypass; renal or aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants; joint replacements; hearing aid; neurostimulator; insulin pump; I.U.D.; being pregnant or trying to become pregnant; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires, or any other metal implants; and permanent eyeliner and/or eyebrows.

Risks of IV Contrast: As part of your treatment, a CT scan may be done. There may be some reactions related to the contrast dye used in CT scans. Contrast dye is usually administered when you get a CT scan. Contrast dye may also be used in MRI scans. Some people may develop hives and itching or other allergic symptoms from this dye, swelling of the heart, cramps of the voicebox, breathing distress caused by narrowing of the airways in lungs, low blood pressure, with loss of consciousness, and in rare cases, severe loss of blood and fluids leading to shock and death, fainting, seizures, and irregular heartbeats. In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

Risks and side effects related to FDG-PET/CT scans:

FDG is the image-guidance for the IG-BMS-IMRT technique. This technique takes approximately 60 minutes longer than the standard technique.

The risks associated with an FDG-PET/CT scan are minimal. FDG is considered safe, and there has not been a report of side effects with this imaging. These scans are an established diagnostic test and often performed for many kinds of cancers.

Rarely, some patients may experience a severe allergic reaction to the radioactive glucose, which can result in hives or difficulty breathing.
There is a risk of discomfort, bruising, bleeding, fainting or infection with the placement or removal of the needle used for drawing blood and injecting the FDG. Some persons may find it uncomfortable to lie still on their back for more than 60 minutes.

There may be other risks associated with participation in this study that are currently unforeseeable.

BENEFITS OF PARTICIPATION IN THIS STUDY

If you agree to take part in this study, there may be a direct medical benefit to you. IG-BMS-IMRT reduces dose to normal organs, which previous studies have indicated may reduce side effects compared to standard radiation therapy. However, the benefits of IG-BMS-IMRT are unknown. Others may also benefit from the information learned from this research study.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY

If you choose not to take part in or stop participating in this research study, there may be other treatments. Refusal to take part in this study will not cause penalty or loss of benefits to which you are otherwise entitled.

You do not have to participate in this study to receive treatment for your cancer. Other possible treatments could include treatment with other drugs or drug combinations, participation in other research studies, or supportive care only (no cancer treatment). Please talk to your doctor about these and other options.

COSTS/COMPENSATION

You or your insurance company/third party payor will be billed for all routine procedures and drugs associated with this study including the cost of treating injuries resulting from such routine procedures. Routine procedures and drugs are those that you would likely receive whether or not you are in this study. You will be responsible for any deductibles or co-payments that are associated with your insurance coverage.

Examples of procedures and drugs that may be billed include the following: diagnostic tests, radiation therapy and chemotherapy. There will be no payment to you for participating in this study, unless you decide to participate in the optional study procedures.

The optional procedures involves 4 separate visits for MRI scans for which you will be paid $100 for each visit.

COMPENSATION FOR RESEARCH-RELATED INJURY

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 657-5100 for more

information about this, to inquire about your rights as a research subject or to report research-related problems.

VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary. If you choose not to participate or wish to withdraw your consent to participate in these study procedures at any time, it will in no way affect your regular treatments or medical care at this institution or loss of benefits to which you are entitled.

You will be informed of any new findings that might affect your willingness to continue participating in the study.

If health conditions occur which would make your participation in this study possibly dangerous, or if other conditions occur that would make participation in this study detrimental to you or your health, then your study doctor may discontinue your participation in this study.

Your study doctor or sponsor may stop your participation in this study at any time without your consent if:

You have side effects that require removal from the study.
You do not comply with the procedures required for study participation
The doctor does not deem participation in the study to be in your best interest.
You refuse therapy according to the terms of the study protocol

DO YOU HAVE ANY QUESTIONS?

Dr. Mell and/or his co-investigator or coordinator has explained this study to you, and has answered your questions. You may contact Dr. Mell at (858) 822-6040. You may also call the hospital 24-hour paging system at (858) 657-7000 and ask for the radiation oncologist on-call. If you have other questions or research-related problems, you may call the Moores UCSD Cancer Center Clinical Trials Office at (858) 822-5354.

If you have questions about your rights as a research participant, your participation in this study, and/or concerns about this study, you may call the UCSD Human Research Protections Program (a group of people who review the research study to protect your rights and welfare) at (858) 657-5100.

CONFIDENTIALITY

The confidentiality of your research records will be maintained to the extent permitted by law. Your medical information will not be made publicly available unless disclosure is required by law or regulation.

Data obtained from this study may be published or given to regulatory authorities, including the Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, the UCSD Institutional Review Board, the Moores UCSD Cancer Center Data and Safety Monitoring Board (DSMB) and other governmental agencies in the United States or other countries in which regulatory approval may be sought. Any potential risk of loss of confidentiality will be minimized.

OPTIONAL Procedures

You may be asked to participate in Image-Guided Bone Marrow-Sparing IMRT using FLT-PET and/or functional MRI during this research study. These images will be used to understand how to better design radiation therapy plans.

FLT-PET involves injection of a radioactive substance intravenously followed by a standard positron emission tomography (PET) scan. There is exposure to a small amount of radiation, much less than the standard doses. There is a risk of discomfort, bruising, bleeding, fainting or infection with the placement or removal of the needle used for drawing blood and injecting the FLT.

There may be a direct benefit to you by consenting to this optional procedure, because the treatment may be given more accurately as a result of this imaging. There may also be a benefit from the medical knowledge gained to patients in the future. There are no additional costs to you for taking part in the optional procedures.

Your study doctor has no personal or financial interest in this research.
Having read and understood the above, and having had the chance to ask questions about these additional, optional procedures, please initial next to your response below:

_____ You give permission to take part in FLT-PET optional procedure.

_____ You do **not** give permission to take part in FLT-PET optional procedure.

_____ You give permission to take part in quantitative MRI optional procedure.

_____ You do **not** give permission to take part in quantitative MRI optional procedure.

_____ _____
Signature of Participant Date

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SIGNATURE AND CONSENT

Your participation in this study is voluntary, and you may refuse to participate or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. You will receive a signed copy of this consent document and a copy of "The Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

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