University of California, Los Angeles
CONSENT TO PARTICIPATE IN RESEARCH

LAY TITLE: A Study of the Safety of an Experimental Drug Combined with Temozolomide and Radiation in Individuals with Malignant Brain Tumors.

PROTOCOL TITLE: Phase II Trial of VELCADE® (Bortezomib) in Combination with Temozolomide and Regional Radiation Therapy for Upfront Treatment of Patients with Newly-diagnosed Glioblastoma Multiforme. [Protocol X05303 Amendment 7 dated 11 Feb 2014]

DEPARTMENT OF NEUROLOGY
PRINCIPAL INVESTIGATOR: Albert Lai, MD, PhD.
CO-INVESTIGATOR: Timothy Cloughesy, MD.
Phioanh Nghiemphu, MD.

▪ INTRODUCTION

You are being asked to participate in a research study conducted by Dr. Albert Lai, Dr. Timothy Cloughesy, and Dr. Phioanh Nghiemphu from the Department of Neurology at the University of California, Los Angeles. This is an investigator initiated multi-center study sponsored by UCLA Department of Neurology. The study drug VELCADE (Bortezomib) will be provided by Millennium Pharmaceuticals, Inc.

You have been asked to participate in this study because you have a newly diagnosed brain tumor. The doctors at UCLA study the nature of disease and try to develop better methods of diagnosis and treatment. This is called clinical research. A total of 50 subjects will be enrolled into this study, with approximately 25 subjects at UCLA.

This study is to evaluate the activity of the experimental drug VELCADE (Bortezomib) when given with the administration of standard radiation therapy and an FDA approved drug Temozolomide.

This consent form contains information that will be discussed with you about the purpose of this study, how your participation may benefit you, the risks of your participation, and what is expected of you. You will be in the study for at least two years or until you experience an unacceptable toxicity, your disease returns or you withdraw your consent. You may continue with study treatment up to two years, if you and your doctor decide that it is in your best interest to do so.

Once you understand the study, and if you wish to participate, you will be asked to sign this consent form. You will be given a copy to keep.

Your participation in this study is entirely VOLUNTARY. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

▪ DISCLOSURE

Your health care provider may be an investigator of this research protocol and, as an investigator, is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your doctor.

▪ PURPOSE OF THE STUDY

The experimental aspect of this Phase II trial involves a combination of a study drug, Bortezomib plus the administration of standard radiation therapy and an FDA approved drug Temozolomide (chemotherapy agent).

The purpose of this study is to find the answers to the following research questions:

1. Is Bortezomib with radiation therapy and Temozolomide safe when given to patients with brain tumor?
2. What are the side effects of Bortezomib when given with radiation and Temozolomide and how often do they occur?
3. Can Bortezomib when given with radiation and Temozolomide be effective in shrinking tumors when given to patients with brain tumors?
4. To determine whether the presence of genetic alterations or specific proteins in the tumor samples can predict whether this study drug is effective on the tumor.

▪ BACKGROUND

Bortezomib is the investigational therapy being administered in this research study. There is increasing evidence that tumor growth may be the result of the overproduction of certain substances made by the body that function to regulate cell division and cell survival, called growth factors. Bortezomib is a proteasome (protein) inhibitor and its primary mechanism of action is inhibition of the cell growth by inhibiting several pathways which are responsible to regulate cell division and cell survival.

Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

Bortezomib has not been approved by the FDA for the treatment of glioblastoma multiforme.

Temozolomide is approved by the FDA for the treatment of certain types of malignant gliomas.

■ PROCEDURES

If you volunteer to participate in this study and sign this consent, we would ask you to undergo the following procedures:

Screening Assessments:

If the study doctor thinks that you may be eligible (qualify) to be enrolled onto this study and you agree to participate, it will be necessary for medical tests and procedures to be performed within a 14-day period before you would be scheduled to receive the study treatment:

- A review of your general medical, cancer history
- A physical examination including height, weight, heart rate, blood pressure, and temperature.
- A neurological evaluation.
- Routine blood taken (approximately 2 tablespoons) to evaluate your blood counts and liver and kidney function.
- If you are a woman of childbearing potential, a blood pregnancy test will be done.
- Urine samples taken.
- You will undergo a brain MRI if you have not had one within a specific period of time to measure the size of your tumor.
- A review of your medications taken currently and within the past 14 days.
- You will be asked to provide pathology slides from your original surgery and a small portion from your saved surgery specimen which will be used for specific studies to examine the effect of study drug on the tumor cells.

Radiation Therapy and **Temozolomide** while on **Bortezomib**

You will come to the UCLA 200 Medical Plaza and to the UCLA General Clinical Research Center (GCRC) for all treatment related visits. The study drug Bortezomib, at a dose of 1.3 mg/kg, will be administered by subcutaneous injection, SQ, (shot into your skin) on Day 1, Day 4, Day 8, Day 11, Day 29, Day 32, Day 36, and Day 39 during radiation therapy. You will start Bortezomib on same day with Temozolomide and the radiation treatment. Each subcutaneous injection will last about 3 to 5 seconds.

If you must stop treatment because of unfavorable side effects, you may be able to restart treatment once the side effect has improved or resolved. Your doctor will discuss with you whether it is in your best interest to continue treatment.

You will receive standard of care radiation therapy for a 6 week period.

During radiation therapy, Temozolomide will be given by mouth 75 mg/m^2 once a day for a six week period (42 days). The last dose of Temozolomide will be taken on the last radiation treatment day. You should take Temozolomide on an empty stomach with water either before eating in the morning or no less than 2 hours after eating or drinking if you take it in the evening before bedtime. The radiation therapy and Temozolomide are considered standard treatment for your brain tumor.

You will have the following exams to monitor the effects of the study treatment:

- Complete neurological & physical exam, during your radiation treatment (every 2 weeks).
- Approximately 1 tablespoonful of blood will be drawn for routine blood tests, every week until you have completed the radiation treatment.
- You will have additional blood samples collected for research purposes approximately 1 tablespoon on days 1 and 29 before administration of Bortezomib. These studies will help the study doctors better understand how Bortezomib works and will help answer the question of whether your response (or lack of response) to Bortezomib is related to your genes. Genes contain the instructions for making living organisms and are contained in DNA. Most DNA is identical among human beings, but the small variations we all have in our DNA may explain why different people have different responses to the same drug.
- You will inform your doctors of any other medications you are taking, including over-the-counter medicines, herbal therapies or medicines or other alternative therapies. There may be interactions between drugs and it is important that your doctors know what you are taking. On the day of your study drug administration you should not take vitamin supplements such as Vitamin C, Alpha Lipoic Acid, any antioxidant, or green tea.

<u>After radiation therapy while on **Bortezomib** and **Temozolomide**</u>

When you have completed radiation therapy, your study doctor will ask you to stop taking Temozolomide and Bortezomib for 2 to 6 weeks (called the rest period). After the rest period, you will re-start Temozolomide on the same day of the next planned dose with Bortezomib. You will receive Bortezomib at 1.3 mg/kg on Day 1, Day 4, Day 8, and Day 11 of a 28 day treatment cycle. The first post radiation Temozolomide dose will be 150 mg/m^2 once a day for 5 days (Days 1 to 5) every 28 days. If you do not have any significant side effects at the end of the first cycle, you may be treated at 200 mg/m^2 for all subsequent cycles. All cycles will consist of 28 days (4 weeks), there is no break between cycles.

Temozolomide dose will not be increased greater than 200 mg/m^2. Bortezomib dose will not be increased greater than 1.3 mg/kg.

Your dose may be reduced temporarily or permanently to adjust for side effects, or drug may be discontinued if you cannot tolerate it.

If you are experiencing unacceptable side effects after the first 12 treatment cycles (after the first year on study) your Bortezomib dosing schedule may be changed to weekly for 3 weeks with 7 days off, and if necessary, to every other week.

This schedule may continue for up to 2 years or until you experience a negative effect, your disease returns, or you withdraw your consent.

You will have the following exams to monitor the effects of the study treatment:

- Complete neurological & physical exam, prior to every cycle (every 4 weeks).
- You will be asked to complete a questionnaire at the beginning of each cycle after your neurological exam (a series of questions to evaluate if you are experiencing any joint or muscle pain and if you have any hearing difficulties, changes in sensation such as

numbness, tingling, discomfort, or weakness in the arms and legs). It will take you about 5 minutes to answer the questions.

- Approximately 1 tablespoonful of blood will be drawn for routine blood tests, before each treatment with Bortezomib on Day 1 and Day 29.
- You will have additional blood samples collected (approximately 1 tablespoon) for research purposes before each treatment with Bortezomib on Day 1 of a 28 day treatment cycle. This will help answer the question of whether your response (or lack of response) to Bortezomib is related to your genes. Genes contain the instructions for making living organisms and are contained in DNA. Most DNA is identical among human beings, but the small variations we all have in our DNA may explain why different people have different responses to the same drug.
- You will undergo a Brain MRI every 8 weeks to measure the size of your tumor.
- You will inform your doctors of any other medications you are taking, including over-the-counter medicines, herbal therapies or medicines or other alternative therapies. There may be interactions between drugs and it is important that your doctors know what you are taking. On the day of your study drug administration you should not take vitamin supplements such as Vitamin C, Alpha Lipoic Acid, any antioxidant, or green tea.

Post Treatment Evaluation

If your tumor grows or spreads while on treatment, if you choose to withdraw from this research study at any time, or if your participation is terminated by your study doctor for any reason, you will be asked to complete a final study visit that will be 30 days after your last study treatment.

At the final study visit, you will have a physical examination and a neurologic evaluation. You will be asked by the study doctor about any health problems you have and medications you take, and you will have a urine sample collected and routine blood samples drawn (approximately 2 tablespoons) for laboratory assessments. You will also have an MRI of your brain to assess your tumor.

If you have an ongoing side effect at the final study visit, you will be contacted every month until that side effect has gone away or stabilized.

After you have stopped receiving study treatment, the research staff will call you or a designated member of your family every 4 months after your last clinic visit to follow your health status.

You will be asked to provide pathology slides and a small portion from your saved surgery specimen if you are scheduled for elective surgery at the time of your treatment failure or any time during your follow-up period, which will be used for specific studies to examine the effect of study drug on the tumor cells. These tests are all optional and for research purposes. Your decision to agree to these optional procedures is entirely voluntary; therefore, if you decide to not agree to these optional procedures, your ability to participate in the research study will not be affected. On the checklist at the end of this form, you are asked to indicate your consent regarding the donation of your samples.

(Please see the study calendar on page 18 regarding all the study procedures requested.)

■ POTENTIAL RISKS AND DISCOMFORTS

Risks Associated with Bortezomib:

Bortezomib should not be taken if you have ever had a serious allergic reaction to Bortezomib, boron, or mannitol. You may experience some risks or discomforts when you are treated with the study drug. You are at risk of having all, some, or none of these symptoms and they may vary in severity. The severity may be mild, moderate or severe, up to and including death. Any symptoms or conditions that you have before you start study drug may get worse. Also, there is always a chance that a risk that is rare or not yet known may occur. If any of these symptoms occur, you must tell your doctor who may give you other drugs to ease discomforts you have. Your doctor may lower or withhold the dose of Bortezomib. If you have a very bad reaction to the study drug, your doctor may permanently stop the study treatment for good.
Other drugs and supplements may affect the way Bortezomib works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

Most Common Bortezomib Risks:

The most common risks are those that have occurred in greater than or equal to 30% of patients who have received Bortezomib:

Feeling weak, tired, and generally uncomfortable.

Gastrointestinal effects such as constipation, diarrhea, nausea, vomiting, and loss of appetite. These may result in dehydration and/or weight loss.

Fever very commonly with shaking chills.

Painful feelings or numbness and tingling in hands and feet which may not get better after stopping Bortezomib. Uncommonly the nerves that control things like your heart rate, gut movement and urinary bladder may be affected

Lowered platelets; that may increase the chance of bleeding .

Anemia (lowered red cells); that may make you feel tired and weak.

Very Common Bortezomib Risks:

The very common risks are those that have occurred in 10-29% of patients who have received Bortezomib:

Lowered white blood cells called neutrophils that may increase your risk of infection and is uncommonly associated with fever; commonly you may have lowered white blood cells called lymphocytes or have lowered red blood cells, white blood cells and platelets at the same time.

Flu-like symptoms and other upper respiratory tract infections, such as chills, sore throat, and runny nose.

Abdominal (belly) pain.

Aches and pains in muscles and joints, back pain.

Swelling and fluid build-up in the arms and legs.

Feeling dizzy. You should not drive or operate any dangerous tools or machines if you have this symptom.

Cough, feeling short of breath, lung infections including pneumonia and commonly bronchitis.

Headache

Skin rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with skin peeling and mouth sores.

Herpes virus such as shingles (herpes zoster) that can sometimes cause local pain that does not go away for a while and herpes simplex virus. Shingles can sometimes spread over large parts of the body. Both may also affect the eyes or brain, but this is uncommon.

Feeling anxious.

Problem in sleeping (insomnia).

Common Bortezomib Risks:

Common risks are those that have occurred in 1-9% of patients who have received Bortezomib:

Lowered blood pressure that can commonly cause you to feel light headed or faint when you stand up.

Changes in heart rate and heart beat that can cause you to possibly feel light-headed, dizzy, faint, short of breath, and/or have chest pain. This may also cause you to feel confused. An uncommon risk is a possible life threatening abnormal heart beat.

New or worsening heart failure, that can show up as feeling short of breath, swelling in the legs, and/or chest pain, or decreased heart function and can uncommonly be severe. If you have heart failure or other diseases that put you at risk of getting heart failure, you should tell your doctor.

Fluid build-up around the lungs.

Infection and/or inflammation of the eye or eyelids.

Blurred vision.

Painful sores of the mouth and/or throat, which may make swallowing difficult.

Heartburn, acid reflux and stomach bloating.

Severe bleeding, including bleeding in the stomach and intestines (gut) that may be linked with low platelet counts, and blood clotting changes. Uncommonly, this bleeding may cause bloody diarrhea and/or bloody vomit.

Nosebleeds

Runny nose.

Kidney function that gets worse.

Fainting.

Change in the way things feel; numbness, tingling.

Muscle weakness.

Weight loss.

Increase in liver enzymes which may indicated liver damage.

Infections of the bladder, sinuses, throat, stomach and intestines (gut), skin and at the area of skin where your catheter is placed.

Itchy rash.

Life-threatening infections in the blood (sepsis).

Changes in blood sugar have been reported in a few diabetic patients who took oral antidiabetic medicine. If you are taking oral antidiabetic medicines you may need your blood sugar levels watched more closely.

Feeling confused.

Changes in the way things taste.

Lowered amount of potassium and sodium in your blood and increase in the amount of calcium in your blood.

Uncommon Bortezomib Risks:

Uncommon risks are those that have occurred in less than 1% of patients who have received Bortezomib:

Inflammation and fluid build-up in the lungs, or fluid or pus build up between the layers surrounding the lungs that may cause breathing problems, and can be life-threatening or lead to death. Increased blood pressure in the lungs, called pulmonary hypertension, has also been reported. This can cause breathing problems and can be life-threatening. If you have new or worsening breathing problems you should tell your doctor.

Inflammation of the layers surrounding your heart or collection of fluid around the heart may cause chest pain or breathing problems and can be life-threatening or lead to death. If you have new or worsening chest pain or breathing problems you should tell your doctor.

Hepatitis, and liver failure (in patients who also got many drugs and had other serious medical problems).

Pain, redness, swelling and infection in the area of the skin where Bortezomib is injected into the vein.

Pain in the mouth and throat when swallowing.

Loss of hearing.

Intestinal obstruction (blockage in the gut) that may get better on its own and not need surgery and inflammation of the intestines, pancreas or stomach.

Coughing up blood.

Bleeding in the brain and subdural hematoma which is bleeding between the skull and your brain.

Fast death of cancer cells that may let toxins into the blood and injure organs, such as the kidneys.

Allergic reactions that may include skin swelling and/or swelling of the face or throat and could be severe or life threatening.

Severe muscle weakness and paralysis (not being be able to move your arms and legs).

Changes to the brain that may cause convulsions and confusion.

Reversible Posterior Leukoencephalopathy Syndrome affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), as well as changes in the brain scan. The risk of RPLS may be increased if you receive Bortezomib in combination with temozolomide and radiation therapy. This condition is usually reversible by controlling the increase of blood pressure with medication. In rare cases, it is potentially life-threatening and may have long term effect on the brain function.

The addition of the Bortezomib to the temozolomide and radiation therapy may cause worsening of your blood counts, such as low platelets in the blood that may result in bruising, bleeding in mucous membrane, wounds or other tissues. If this happened, you may require blood transfusion. A drop in the blood counts, in particular, a decrease in the number of neutrophils in the blood (a type of white blood cells that helps fight infection), may result in severe infections such as pneumonia that may require IV antibiotics and medications to increase your white blood cells. This could potentially lead to a hospital stay. This can be serous or life threatening.

Opportunistic infections (may occur when Bortezomib and temozolomide is used in combination with radiation treatment and steroids). An infection caused by an organism that usually does not cause illness, but causes disease when a person's immune response (resistance) to infection is impaired. You will be very closely monitored for any signs or symptoms in order to avoid those type of infections and you may be placed on antibiotics if needed.

Optic neuropathy (damage to the optic nerve which can cause changes in vision, to include blindness)

Blindness

Progressive multifocal leukoencephalopathy (PML). A very rare disorder that damages the material called myelin that covers and protects nerves in the brain. The disorder is caused by a virus that most people have been infected with by the age of 10 but hardly ever causes symptoms unless you have a weakened immune system. Symptoms may include headache, loss of coordination, loss of language ability, memory loss, vision problems, weakness of the arms and legs that gets worse. This condition is treated by strengthening the immune system, but is often irreversible and can be a life threatening condition.

Reproductive Risks: Temozolomide has been shown to cause birth defect in animals. The effects of Bortezomib on a fetus are unknown and may be harmful; therefore, you should not become pregnant or father a child while in this study. You must use a highly effective birth control method or a combination of 2 additionally effective birth control methods while in this study, and for at least 30 days after the last dose of study medication. Examples of highly effective birth control are a condom or a diaphragm, either with spermicidal jelly; oral, injectable, or implanted birth control; or abstinence. The effect of Bortezomib on reproduction and its safety in pregnancy are unknown. If you are a woman capable of becoming pregnant [anyone who has not undergone a hysterectomy (removal of the womb), has not had both ovaries removed or has not been post-menopausal (stopped menstrual periods) for more than 24 months in a row], you must have a negative pregnancy test before beginning treatment. If you are pregnant, you cannot be in this study because of possible harm to the fetus. If at any time during the study you suspect that you have become pregnant, please notify the study doctor immediately. If you are a male and your partner becomes pregnant during the study, you should also notify the study doctor immediately. The study doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. You should also notify the doctor managing your pregnancy that the mother/father received a study drug.

If you are a female study subject and you become pregnant during your participation in this study, your treatment with study drug will be stopped and you may be withdrawn from some of

the study procedures but not from follow-up by your study doctor. The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy.

If you are a male study subject and your partner becomes pregnant, the study doctor will ask for your partner's permission to collect information about her pregnancy and the health of the baby.

Laboratory tests show that Bortezomib may damage DNA. Based on this information, it is possible that Bortezomib may cause infertility in men and women (not being able to become pregnant or father a child).

You should not nurse (breastfeed) a baby while on this study because Bortezomib and Temozolomide may enter breast milk and possibly harm your child.

Risks of Blood Sampling: Blood samples for laboratory and drug analysis will be obtained either by venipuncture (a needle that will be inserted into a vein in your arm) or by indwelling catheter (a large needle with a long tube attached into a large vein in either your arm, neck or above your collar bone). Typical risks of venipuncture include pain, bruising or transient bleeding at the venipuncture site. Typical risks of an indwelling catheter may include pain, bruising, or transient bleeding upon removal; infrequent risks may include reduced clotting (if heparin is used), infection, or a low potential for clots to form at the catheter site.

Other Side Effects: As with any experimental drug, there may be adverse events or side effects that are currently unknown and some of these unknown risks could be permanent, severe, or life threatening.

▪ ANTICIPATED BENEFITS TO SUBJECTS

There is no guarantee that this study will benefit you in any way.

▪ ANTICIPATED BENEFITS TO SOCIETY

This study will provide information about how the study drug works in the body, which may benefit future patients. It is hoped that information gained in this study will aid in the understanding of cancer and help in the development of new approaches to its treatment.

▪ ALTERNATIVES TO PARTICIPATION

You may choose not to take part in this study. Other medical therapies are available for the treatment of your brain tumor, including Chemotherapy (such as Carboplatin, Temozolomide, BCNU, PCV or Etoposide), hormone therapy (Tamoxifen), radiation therapy, additional surgery, Gliodal wafers, or other experimental protocols are alternatives. Also, you could choose not to have therapy at this time, except care to treat your symptoms and help you feel more comfortable. Please talk to your doctor about these and other options.

▪ PAYMENT FOR PARTICIPATION

There will be no payment, gifts or other compensation for your participation in this study. You will receive a voucher for UCLA parking for study-related visits.

▪ POSSIBLE COMMERCIAL PRODUCTS

All tissue and/or fluid samples are important to this research study. Your sample will be owned by the University of California or by a third party designated by the University (such as another university or a private company). If a commercial product is developed from this research project, the commercial product will be owned by the University of California or its designee. You will not profit financially from such a product.

▪ SAMPLE REMAINING AT THE END OF THE STUDY

On the checklist at the end of this consent form, you will be asked to indicate if you would permit part of this sample to be shared with other researchers. If you agree to have your sample shared with other researchers and later decide to withdraw, we may not be able to retrieve any or all of your sample from other researchers. The researcher is not required to store your sample(s) indefinitely.

▪ INFORMATION ABOUT YOUR SAMPLE

On the checklist below, you are asked to let us know if you would like to receive information about the results of this study. There are two types of information you may receive:

1. general information about what this study found (or conclusions of the study);
2. specific information about what the study found about your sample.

You may also choose not to receive any information. Research is a long and complicated process. Obtaining general information from a project may take years. Even if there is general information from a project, there may not be personal information for every participant.

▪ FINANCIAL OBLIGATION

You will not be charged for any materials, services, or procedures that are solely for research purposes during this study, i.e., the study drug Bortezomib, pharmacy-dispensing fees, neurological exams, and parking fees for study related visits.

There is no cost to you for the drug Bortezomib itself, however, you will be paying for the costs of routine physical exams, routine neurological exams, routine blood tests, routine MRI scans, and doctor's fees associated with your routine medical care such as radiation therapy and Temozolomide. You or your insurance company must cover the costs of the treatments that are considered standard of care for your disease. The following are considered standard of care for your condition: radiation therapy, Temozolomide, physician visits, blood tests, and MRI scans. You are entitled to receive an estimation of the costs associated with this study before you enroll.

It is possible that your insurance will not pay for all the treatments and tests you will receive if you participate in this research. That is because many insurance companies, HMOs, and health benefit plans do not cover the cost of standard treatments that are provided as part of a research study. If that happens, you will be responsible for all charges relating to your treatment including cost of the medication, pharmacy dispensing fees, office visits, laboratory charges, radiological studies, and hospitalization charges (if necessary).

▪ EMERGENCY CARE AND COMPENSATION FOR INJURY

If you are injured as a direct result of research procedures, you will receive treatment at no cost. The University of California does not normally provide any other form of compensation for injury.

▪ PRIVACY AND CONFIDENTIALITY

The only people who will know that you are a research subject are members of the research team and, if appropriate your physicians and nurses. No information about you, or provided by you during the research, will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

Authorized representatives of the Food and Drug Administration (FDA), Millennium Pharmaceuticals, Inc. (which is providing study drug for this study), study monitors, and the UCLA Office of the Human Research Protection Program (OHRPP) may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others. You will also be asked to sign a separate authorization for the use and disclosure of your personal health information.

The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify you. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

▪ GENETIC INFORMATION IN YOUR SAMPLE: POSSIBLE LIMITS TO CONFIDENTIALITY

Every tissue or fluid sample contains genetic information. Recent studies have found normal and disease producing genetic variations among individuals. Such variations may permit identification of individual participants. Despite this possible limitation, every precaution will be taken to maintain your confidentiality now and in the future.

We have learned from past research that we will not always be able to predict future research findings and new technologies. You should be aware that unforeseeable problems may arise from new developments.

Sometimes genetic information suggesting different parentage is obtained during research. We do not plan to report such findings to participants.

Within the limits imposed by technology and the law, every effort will be made to maintain the privacy of your genetic information

▪ PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at UCLA.

▪ CONSEQUENCES OF WITHDRAWAL

You may withdraw at anytime and are under no obligation to have any further treatment or procedures. Withdrawal from this study will not affect or interfere with your routine care for your disease.

▪ WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience serious side effects, or if you become ill during the research, you may have to drop out, even if you would like to continue. The principal investigator, Dr. Albert Lai, will let you know if it is possible to continue. The decision may be made to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate. Participation in this study may be terminated by the investigator at any time without regard to your consent if it is felt that this course of action is in your best interest, or if you violate study requirements, or for administrative reasons.

▪ NEW FINDINGS

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

▪ IDENTIFICATION OF INVESTIGATORS

Albert Lai, MD., Timothy Cloughesy, MD., and Phioanh Nghiemphu, MD. at 710 Westwood Plaza, RNRC 1-230, Los Angeles, CA 90095-1769, (310) 825-5321 are available to answer any questions

you may have regarding this research study. In the event of a research-related emergency Dr. Lai, Dr. Cloughesy and Dr. Nghiemphu can be reached 24 hours a day, 7 days a week, through the UCLA page operator, at (310) 825-6301.

■ RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research subject, you may contact the Office of the Human Research Protection Program (OHRPP), 11000 Kinross Avenue, Box 951694, Los Angeles, CA 90095-1694, (310) 825-5344.

SIGNATURE OF RESEARCH SUBJECT

I have read the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

_____
Name of Subject

_____ _____
Signature of Subject Date

■ Donating Samples for Additional Research

Please indicate by checking and initialing below, if you agree or not to allow the sponsor to test your samples for additional research purposes.

_____ I consent on donating my samples for additional research purposes.

_____ I do not consent on donating my samples for additional research purposes.

Please indicate by checking and initialing the category below what type of information you want to receive. It is your responsibility to let the investigator know if your address and/or telephone number changes. The contact information is in this informed consent form under "Identification of Investigators".

_____General Information about what the study found

_____Specific Information about what the study found about me

_____I do not want any information about my sample

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____
Name of Investigator

_____ _____
Signature of Investigator Date (must be the same as subject's)

Appendix A: Potential Risks and Discomforts for Standard of Care

Side Effects Associated With Temozolomide:

Common Side effects

- Nausea and vomiting
- Fatigue
- Constipation
- Loss of appetite
- Decrease in the number of platelets (cells causing clotting). This may cause bruising or bleeding. If the platelets are very low you may need a transfusion or other treatments.
- Decrease in the number of white blood cells which may rarely result in life-threatening infection.
- Decrease in the number of red blood cells (cells that carry oxygen throughout the body). This may make you feel tired or weak, or have difficulty breathing. If the decrease is severe you may need a red blood cell transfusion or other treatments.
- Fever
- Back pain
- Abdominal pain

Less Common Side Effects

- Headache
- Rash
- Hair loss
- Itching and burning
- Diarrhea
- Fatigue
- Insomnia (difficulty sleeping)
- Amnesia (loss of memory)
- Parasthesias (numbness and tingling in extremities)
- Hemiparesis (weakness on one side of the body)
- Edema (swelling)

Rare Side Effects

- Altered consciousness
- Sore throat
- Liver damage
- Kidney damage
- Allergic reactions
- Convulsions (seizures)

Risk from Radiation Therapy: The risks of radiation therapy include some or all of the following side effects: scalp redness or soreness, hair loss which may be temporary or permanent, dry mouth or altered taste, hearing impairment, fatigue, sleepiness or temporary aggravation of the tumor symptoms. These may include headache, seizure and/or weakness or changes in mental function. There is a risk of injury to the eyes from radiation therapy with the possibility of blindness. Since radiation procedures are all standard of care, the amount of radiation received by the participant is the same as that for similar patients who are not on protocol. Therefore, there is no increased risk of radiation exposure by participating in the study.

Risks of MRI: Recently, it has been reported that a rare but serious adverse reaction called nephrogenic systemic fibrosis (NSF) may occur after exposure to the gadolinium-based contrast agent gadodiamide (Omniscan®, GE Health Diagnostic, Amersham, United Kingdom). Nephrogenic systemic fibrosis is a condition wherein patients develop large areas of hardened skin with lesions called plaques and papules with or without skin discoloration. In some cases, NSF could lead to physical disability and may involve not only the skin, but also the liver, lungs, muscles and heart. The typical patient in whom this has occurred is middle-aged and has end-stage kidney disease.

APPENDIX B: STUDY CALENDAR

Evaluation during the Radiation therapy:

Procedures	Prior to Treatment	Every Week	Every 2-Week	Every 4-Week	At week 6
History, Physical Exam, Height/Weight	X [(a)]		X	X	X
Neurologic Evaluation	X [(a)]		X	X	X
Routine Blood Test	X [(a)]	X		X	X
Urine Test	X [(a)]			X	
Research Blood Test [(b)]	X			X	
MRI head	X				
Pregnancy Test [(c)]	X				
Pathology Slides/Frozen Tissue	X				
Bortezomib [(d)]			X		
Temozolomide [(e)]		Days 1 - 42			
Radiation Therapy [(f)]		X for 6 weeks			

Evaluation to be Obtained During Bortezomib and Temozolomide after Radiation

Procedures	Day 1	Day 21
History, Physical Exam, Height/Weight, Toxicity	X	
Neurologic Evaluation	X	
Routine Blood Test	X	X
Research Blood Test [(b)]	X	
MRI Head [(g)]		
Bortezomib	X (Days 1, 4, 8, 11)	
Temozolomide	X (Days 1 - 5)	

(a) Must be obtained within 14 days prior to starting treatment.
(b) Research blood test (on day 1 of a 28 days treatment cycle).
(c) for female patients.
(d) Bortezomib on Days 1, 4, 8, 11, 29, 32, 36 and 39 during radiation therapy.
(e) Temozolomide Days 1 – 42 during radiation therapy.
(f) Radiation therapy weekly for six weeks.
(g) MRI will be done 2 weeks after the end of the radiation therapy then every 8 weeks.