A PHASE II STUDY OF BEVACIZUMAB AND ERLOTINIB AFTER RADIATION THERAPY AND TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME WITHOUT MGMT PROMOTER METHYLATION (IRB #19965)

Malignant gliomas are the most common brain tumor in adults with about 15,000-17,000 new cases each year in the United States. The typical median survival is approximately 12 months for patients with newly diagnosed glioblastoma (GBM) and 24-36 months for patients with anaplastic astrocytoma. Current standard therapy can treat this type of cancer but in most cases the tumor returns. Standard therapy is radiation therapy combined with temozolomide. This treatment works best for patients who have a certain gene called MGMT turned "off" (methylated).

This study involves the combination of radiation therapy and temozolomide as part of normal standard therapy. The patient's tumor will be tested for MGMT status. If the MGMT gene is not turned "off", subjects will be treated with Avastin (which inhibits blood vessel growth) and Erlotinib (Tarceva—which inhibits a receptor called EGFR). If the MGMT gene is turned "off", subjects will receive standard of care therapy.

Avastin has been approved by the Food and Drug Administration (FDA) for colon cancer, breast cancer, and lung cancer and has reported activity in brain tumors. Erlotinib has been approved by the FDA for lung cancer and pancreatic cancer. Avastin and Erlotinib have not yet been approved by the FDA for glioblastoma and are considered investigational. The purpose of this study is too evaluated whether this combination is better than maintenance with temozolomide after radiation therapy.

Once a patient signs the main consent form, tissue used to confirm diagnosis or surgery will be sent for MGMT analysis to determine whether or not the gene is "on" or "off". Please note, patients who do not have tissue available for central review will not be eligible to participate in this study. While this analysis is taking place, subjects will begin standard treatment (with radiation and temozolomide) for 7 weeks. Once the 7 week standard therapy is complete, subjects will have an MRI done. If the results of the MRI show that the tumor has remained stable or has decreased in size, the subject may continue on trial. If the tumor has grown, subjects will not be allowed to participate in this trial. It is at this point that the analysis of the MGMT gene in the tumor will be shared with the subject. If the MGMT gene is not active in the subject's tumor, the subject will be removed from the study and will continue to receive standard of care treatment for their condition. If the MGMT gene is active in the subject's tumor, the subject will be given Avastin every 2 weeks as an intravenous infusion (over 30-90 minutes) and will take Erlotinib orally daily. Patients will remain on the study for up to one year as long as the study treatment is working. The following procedures will also be done during subject's participation in this trial:
• A pregnancy test (if female of childbearing potential) will be done before the first cycle of treatment. A blood sample (about 1 teaspoon of 5 mL) will be taken.

• Electrocardiogram (EKG—a test that measures the electrical activity of the heart) may be done before first cycle if deemed medically necessary by the study doctor.

• Neurological exam (including blood pressure and heart rate) will be done on Day 1 of each cycle.

• Urine test will be done Day 1 of each cycle.

• Blood test (approximately 2-3 teaspoons or 10-15 mL) will be done Day 1 of each cycle.

• Subjects will be asked to record any side effects they experience

• MRI with contrast (including optional MR Perfusion) will be performed every 2 cycles.

Approximately 10 subjects will take part in this research study at Cedars-Sinai. A total of 50 subjects will participate in the study nationwide. Please note that the subject and their insurance company will not be charged for the study drugs (Avastin and Erlotinib) given in this trial. However, while the study team will supply the subject with these drugs, the subject or their insurance company will be responsible to pay for the administration of Avastin. Depending on the time frame of the subject's enrollment, there may be one MRI that falls outside of standard of care procedures. If this is the case, the MRI will be considered a research related procedure and will not be charged to the subject or their insurance company. All other procedures are considered standard of care and will be billed to the subject or their insurance company.

Patients will be followed-up by the study doctor and staff every 3 months until death, if possible. These follow-up visits are considered standard of care. If a patient chooses to no longer come into the clinic, a member of the study staff will call the patient to determine survival.

This is an Investigator Initiated study developed at Northwestern University (Northwestern University holds the IND). Genentech is providing the study drugs, Bevacizumab and Tarceva. Tissue for MGMT analysis will be de-identified and sent to Maryland to be centrally reviewed. The Brain Tumor Trials Collaborative (BTTC) at the University of Texas MD Anderson Cancer Center will serve as the coordinating center in this trial. No identifying information will be sent to any of these sites in this trial.

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