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**A PHASE I/II TRIAL OF BIBW2992 WITH OR WITHOUT DAILY  
TEMOZOLOMIDE IN THE TREATMENT OF PATIENTS WITH RECURRENT  
MALIGNANT GLIOMA (IRB# 15218)**

Gliomas are tumors that occur in the glial cells, which help support and protect critical areas of the brain. Conventional treatment of malignant gliomas consists of surgery, radiotherapy and chemotherapy, which may provide symptom relief and extend survival for a short period of time. Currently, there is no standard treatment for recurrent glioblastoma multiforme (GBM). The purpose of this Phase I/II research study is to see if BIBW 2992 alone or BIBW 2992 given with temozolomide is as effective and safe as when temozolomide is given alone in patients with recurrent brain tumors.

BIBW 2992 belongs to a group of drugs that can affect the function of special proteins called growth factor receptors that are found on the surface of many cancer cells. A receptor is like a lock to which a matching drug fits like a key. The particular growth factors that BIBW 2992 will fit are called EGR (Epidermal Growth Factor) and HER2 (Human Epidermal Growth Factor Receptor). When these receptors are stimulated, the growth of the cancer cells bearing the receptors is accelerated. In contrast, BIBW 2992 is thought to turn off the function of the EGF and HER2 receptors, leading to slowing of growth and even causing some of these cancer cells to die.

The Phase I portion of this trial is an open-label, single arm seeking to determine the maximum tolerated dose of BIBW 2992 administered with temozolomide in patients with recurrent malignant gliomas (WHO grade III or IV).

Phase II part is an open-label, randomized study that aims to estimate the efficacy and safety of BIBW 2992 alone, with temozolomide, and compared to temozolomide alone in patients with recurrent glioblastoma multiforme (GBM).

Approximately 150 patients will be enrolled in this phase I/II trial sites, 12 subjects will be enrolled at CSMC.

The Phase I portion of the study will enroll six patients that will be entered sequentially into each dose level. In the Phase II portion of the study, 6 patients will be assigned by chance into one of three treatment groups. Group 1 will receive temozolomide alone for 21 days of a 28 day cycle; Group 2 will receive BIBW 2992 for 28 days of each treatment cycle; Group 3 will receive BIBW 2992 for 28 days along with temozolomide for 21 days of a 28 day cycle.

Patients with malignant gliomas who have disease that is worsening or recurring despite standard therapy or surgery and radiotherapy, and who may or may not have had chemotherapy or other forms of treatment will be eligible for the study if they meet entry requirements. For Phase I, patients with recurrent malignant glioma may be included. For Phase II, only patients with recurrent glioblastoma multiforme will be eligible.

Patients taking part in Phase I, will not be eligible to take part in Phase II. For both Phase I/Phase II, subjects will initially be screened to see if they are able to be in this study. During the treatment period for Phase I, subjects will receive the study drug (BIBW 2992) along with temozolomide. For subjects who take part in the Phase II trial, treatment period will consist of either BIBW 2992 alone, BIBW 2992 with temozolomide, or temozolomide alone. For both Phase I/II, each treatment period is 28 days long and is called a "cycle." When the study drug is stopped for good, subjects will come in for an end of treatment visit and a follow-up visit.

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