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### **CILENGITIDE FOR SUBJECTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME AND METHYLATED MGMT GENE PROMOTER—A MULTICENTER, OPEN-LABEL, CONTROLLED PHASE III STUDY, TESTING CILENGITIDE IN COMBINATION WITH STANDARD TREATMENT (TEMOZOLOMIDE WITH CONCOMITANT RADIATION THERAPY, FOLLOWED BY TEMOZOLOMIDE MAINTENANCE THERAPY) VERSUS STANDARD TREATMENT ALONE (IRB #17392)**

Gliomas account to 40% to 70% of all primary brain tumors. Glioblastoma multiforme (GBM) represents the most malignant of these tumors. Conventional treatment for primary disease includes surgery, radiotherapy, and chemotherapy. However, despite these various treatments, patients suffering from glioblastoma multiforme have a poor prognosis with a median survival time of 12-15 months.

Cancer cells that overexpress a protein called O-6-methylguanine-DNA methyltransferase (MGMT) are harder for temozolomide, a chemotherapy, to kill. Cells that contain no MGMT protein because the gene that produced the protein was switched off succumbed more readily to the drugs. Findings from preliminary clinical trials for GBM patients suggested that patients treated with temozolomide and radiation survived longer if the MGMT gene was silenced.

Cilengitide is an experimental drug that is being tested to see if it will extend progression free survival. Prior studies have suggested that cilengitide might cut off the blood supply to tumors, which may prevent tumor growth.

The primary purpose of this study is to test the experimental drug, cilengitide, to find out whether taking cilengitide (2000mg twice weekly i.v.) in addition to standard treatment for glioblastoma can extend overall survival compared to standard treatment alone.

The secondary objectives of this study are:

- To compare Progression Free Survival (PFS) time between treatment groups.
- To investigate safety and tolerability.
- To investigate the population PK of cilengitide.
- To measure subject Quality of Life (QoL) by the EORTC-QLQC30 + QLQ BN 20, general health status by the EQ-5D, health care resource utilization, and work status.

Approximately 504 patients will be enrolled at sites all over the world, 12 patients will participate at CSMC.

A pre-test will be performed to identify MGMT status and determine if the patient is eligible to participate in the study. The pre-test will investigate a specific region of the patient's genetic information, so called MGMT-gene status, which is thought to be associated with the response to study treatment. The pre-test will be run on a tissue sample from the patient's brain tumor. The tissue will be collected (or may have already been obtained) part of the patient's clinically indicated brain tumor surgery. Patient must provide consent to allow permission for the pre-test.

Subjects with newly diagnosed GBM and with methylated MGMT gene promoter, who will be randomized in two groups as follows:

- Cilengitide group: cilengitide + radiotherapy (RTX)/temozolomide (TMZ), followed by cilengitide + TMZ.
- Control group: RTX/TMZ, followed by TMZ.

Subjects in the cilengitide group will be treated with 2000 mg cilengitide (twice weekly, i.v.) in combination with standard therapy for 8 months, followed by a 10 month cilengitide maintenance treatment.

Subjects in the control group will receive standard therapy for 8 months (6 weeks of RTX + TMZ, followed by 6 four-weeks-cycles TMZ maintenance treatment).

Treatment may stop earlier than planned due to occurrence of progressive disease (PD) or unacceptable toxicity, or withdrawal for any other reason. Subjects in the cilengitide group may continue receiving cilengitide after completion of 18 months of cilengitide treatment, until occurrence of PD or unacceptable toxicity, or until withdrawal for any other reason.

In case of intolerance to one of the agents, treatment according to protocol with the other agent or RTX should continue, e.g. in case of early discontinuation of TMZ due to hematological toxicity, subjects may continue receiving cilengitide as per protocol. Regardless of treatment status subjects remain on study for PFS follow up until occurrence of PD or unacceptable toxicity or withdrawal for any other reason.

Participants may be included in an optional genetic research study, for which separate consent will be required. The purpose of the genetic research study is to identify if there are genetic markers which may help in predicting the response to treatment with cilengitide. When used on a larger scale, this research could also allow the development of more effective treatments for patients who suffer from cancer. Currently no information is available regarding the influence of human genetics on cilengitide treatment.

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