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Survival of patients with recurrent malignant brain tumor (glioblastoma multiforme) treated with surgical resection and local chemotherapy using impregnated wafer (Gliadel®) in relation to a clinical predictor; the methylation of methylguanin-DNA-methyltransferase (MGMT) promotor

Submission date 21/09/2015	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 06/04/2016	**Overall study status** Completed	
Last Edited 19/08/2022	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

Primary brain tumors are classified according to their grade (WHO classification I-IV), which is determined by pathologic evaluation of the tumor (i.e. testing to see how advanced the tumor is). The tumors are divided in low grade and high grade gliomas. Low grade gliomas (WHO grade I- II) have a better prognosis than high grade gliomas (WHO grade III-IV). Glioblastoma multiforme is the most common and most aggressive primary brain tumor (WHO grade IV). Despite all the care taken to treat the tumor the disease remains incurable. Less than 10 % of patients survive for 4-5 years. The goal of the treatment is to maintain the quality of life and to increase the survival time. The current standard of care includes surgery and radio-chemotherapy. The success of this treatment can depend on age of the patient (with better results for people under 50 years) and general well-being. In addition, surgery should include ideally a total resection (removal of the tumor) that means that no tumor cells remain after the operation. Unfortunately this is not possible in all cases and depends on tumor location, tumor size and number of tumors. After surgery, the patient receives radiotherapy for a total of six weeks and continuous daily chemotherapy drugs (alkylating nitrosourea agent- temozolomide) . This is followed by six monthly cycles of temozolomide chemotherapy. The benefit of temozolomide chemotherapy depends on the repair enzyme activity- 06-methylguanine-methyltranferase (MGMT). It is associated with tumor resistance (making the tumor respond less well to chemotherapy) because of the fact that MGMT reverses the impact of temozolomide. Inactivation of MGMT gene in the tumor tissue by methylation of the promotor region has been associated with good results in clinical studies. Thus, the methylation of MGMT is a strong predictor for therapy success. In case where the tumor comes back (recurrence) no standard of

care is established. One option is treatment using Gliadel ® implants, small wafers that, once placed in the brain, dissolve slowly, releasing the chemotherapy drug carmustine into the brain tissue. Gliadel® can also be used in tumor resections. It is thought that that the MGMT methylation status also becomes important in the success of this treatment. Up to now, this area has not been well-researched – particularly in terms of whether there is a threshold value the MGMT promotor methylation (i.e. the amount of MGMT promotor methylation that is present) that can be used to predict whether tumor will respond to therapy. This study is being done to find out this threshold value. The goal is to use this information to tailor the therapy regime for individual patients.

Who can participate?
Adults diagnosed with a recurrent glioblastoma multiforme.

What does the study involve?
After checking whether they are eligible, all patients are treated with the Gliadel® implant. They attend follow-up visits after 3, 6 and 12 months where they have a clinical examination, have their quality of life assessed and, if it's thought necessary, they may have a CT or MRI scan. Tissue examples are also taken from each patient to evaluate the methylation of the MGMT promotor.

What are the possible benefits and risks of participating?
The benefit for the patient is a close meshed survey and the probable survival benefit of the Gliadel (Carmustine Wafer). There are no additional risks factors for the patient in comparison to patients not participating in the study, because the therapy regime is commonly used and main goal is to obtain a methylation rate of the MGMT Promotor. To get this information the tumor tissue is investigated.

Where is the study run from?
The leading centre of the trial is the Unfallkrankenhaus Berlin (Germany). A total of four centre's participate in this study- Unfallkrankenhaus Berlin, Department of Neurosurgery, Dietrich-Bonhoeffer-Klinikum Neubrandenburg, Department of Neurosurgery, Vivantes Klinkum Neukölln, Department of Neurosurgery, Universitätsklinik Göttingen, Department of Neurosurgery.

When is the study starting and how long is it expected to run for?
June 2014 to December 2021

Who is funding the study?
Archimedes Pharma Germany GmbH

Who is the main contact?
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Study information

Scientific Title
Survival of patients with recurrent glioblastoma multiforme treated with local carmustine wafer (Gliadel®) in relation to the methylation of methylguanin-DNA-methyltransferase (MGMT) promotor

Study objectives
The methylation of O6-methylguanine-DNA-methyltransferase (MGMT) appears to have a predictive value for recurrent glioblastoma (GBM) patients treated surgically with carmustine-impregnated, biodegradable copolymers (Gliadel ®). The aim of this study is to investigate the threshold of MGMT methylation status to predict the benefit of using carmustine wafer in recurrent glioblastoma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee Charité - University of Berlin, 05/08/2015, ref: EA1/202/15

Primary study design

Observational

Study design
A multicentre observational trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Recurrent glioblastoma multiforme WHO IV, primary treated by surgical resection and radiochemotherapy.

Interventions
Male and female subjects ≥18 years with the first recurrent manifestation of a malignant glioma that have undergone min. one cycle of the Stupp scheme after surgical treatment of the initial manifestation. The diagnosis of glioma recurrence will be established by the findings of contrast enhanced MRI. The indication for revision surgery follows the usual balancing of risks and benefits of the therapy, informed consent and, finally, decision of the patient. Eligible patients will be included after informed consent and will be treated with the investigational implant. All patients will be treated in the same way. Except minor modifications among different hospitals, the different operative steps (tumor resection, wafer placement, access routes) will be standardized as much as possible (maintaining the therapeutic equality). Surgeons and nurses at collaborating centres will undergo hands-on training with wafer implants prior to patient enrolment and operating theatres will be stocked with handling manuals. Study documentation resembles clinical practice and calls for follow-up visits at 3, 6 and 12 months, all of which include clinical examination, recording of quality of life scales, and, if deemed necessary, a cerebral CT or MRI scan. CT or MRI scans will be independently rated by two investigators to verify compliance with trial entry criteria, and to detect violations with exclusion criteria. The tissue sample of the primary operation will be investigated by pyrosequencing to evaluate the methylation of the MGMT promotor.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Overall survival (measured by the date of resection and carmustine wafer implantation and time of death) in relation to the methylation of the MGMT promoter

Key secondary outcome(s)
1. Progression free survival after first revision surgery measured by the recurrence criteria (MacDonald) in cerebral CT and MRI scans in follow-up visits at 3, 6 and 12 months
2. Quality of Life (generic: Short-Form [SF] 36) at one year of follow-up
3. Complication rates (edema, infections, bleeding, surgical revisions for all causes, serious adverse events [SAE]) throughout the study

Completion date
31/12/2021

Eligibility

Key inclusion criteria
1. First recurrent manifestation of a glioblastoma multiforme
2. Female and male ≥18 years
3. Previous adjuvant radio-chemotherapy chemotherapy in accordance with the ”Stupp protocol"
4. The indication for revision surgery follows the usual balancing of risks and benefits of the therapy, informed consent and –finally- decision of the patient

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Patients who underwent more than one surgical revision of malignant glioma
2. Previous implantation of carmustine wafer (Giadel ®)
3. More than six cycles of the Stupp scheme (radio-chemotherapy)

Date of first enrolment
01/10/2015

Date of final enrolment
31/12/2020

Locations

Countries of recruitment
Germany

Study participating centre
Unfallkrankenhaus Berlin, Department of Neurosurgery
Warener Straße 7
Berlin
Germany
12683

Study participating centre

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Sponsor information

Organisation
Unfallkrankenhaus Berlin

ROR
https://ror.org/011zjcv36

Funder(s)

Funder type
Industry

Funder Name
Archimedes Pharma Germany GmbH

Results and Publications

Individual participant data (IPD) sharing plan

Not provided at time of registration.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	In German	19/05/2015	19/08/2022	No	No