**Trial Description**

**Title**
Temozolomid (One Week on/One Week Off) Versus Strahlentherapie in Der Primärtherapie Anaplastischer Astrozytome Und Glioblastome Bei älteren Patienten: Eine Randomisierte Phase III-Studie (Methusalem)

**Trial Acronym**
Methusalem

**URL of the trial**
[---]*

**Brief Summary in Lay Language**
The study aims to optimize the treatment of elderly subjects (> 65) with anaplastic astrocytoma and glioblastoma. Current treatment policies tend to be no more than palliative. There is no consensus as to how radical the surgery should be. Involved-field radiotherapy is the treatment most likely to be accepted apart from supportive and palliative measures. The role of chemotherapy is barely defined. Study data available to date does not suggest that this patient population would benefit from combined radiochemotherapy.

The aim of the study is to verify the hypothesis that first-line chemotherapy with one week on/one week off temozolomide is not inferior to extended-field radiotherapy in the first-line treatment of anaplastic astrocytoma and glioblastoma in the elderly (> 65 age group). The primary endpoint is median survival, as life expectancy is limited to several months. Secondary endpoints are response rates in both arms (CR, PR, MacDonald et al. 1990), median progression-free survival, 1-year and 2-year survival rates, definition of MGMT as molecular genetic prognostic or predictive markers, and quality of life. Theoretically, it should be possible to preserve quality of life in the first-line chemotherapy arm of the study.
This study is a prospective, randomized Phase III intervention study. Following histological documentation of the diagnosis by biopsy or resection of an anaplastic astrocytoma or glioblastoma, patients will be randomized either to receive postoperative extended-field radiotherapy (arm A) or to receive postoperative chemotherapy with temozolomide (arm B).

Randomization will be done for all sites at the CRO, Alcedis GmbH.

For patients intending to participate in the study, the procedure is as follows:

- Request a reference neuropathological review from the brain tumor reference center in Bonn (Prof. Dr. G. Reifenberger) through the local neuropathology department. This review need not be present at randomization because anaplastic astrocytoma and glioblastoma cases are eligible.

- Contact: Prof. Dr. W. Wick, Dep. Neurooncology, National Center for Tumor Diseases and Neurology Clinic, University of Heidelberg, wolfgang.wick@med.uni-heidelberg.de or CRO: Alcedis, Giessen at Alcedis GmbH, I. Helm, Winchester Str. 2, 35394 Gießen, Tel.: 0641 944360, Fax: 0641 94436 70, E-mail: ihe@alcedis.de

- Provide written confirmation that the patient signed the ethics committee-approved consent form.

- Submit the registration form and a copy of the EORTC-QLQ given in Annexes.

In subjects with progressive or recurrent disease, the investigating site will verify whether specific tumor treatment is justified. If yes, chemotherapy with temozolomide is recommended in arm A, possibly after further surgery. Subjects in arm B will receive radiotherapy, possible after further surgery. As all-cause mortality is the primary endpoint, all therapeutic measures following first-line therapy should be documented.

If study treatment is discontinued (first-line therapy) because of progressive disease or if progression occurs after completion of study treatment, the pertinent images should be submitted to the reference center for neuroradiology in Tübingen for reference review.

The treatment modalities employed in the study are chemotherapeutic and radiotherapeutic.
procedures licensed in the Federal Republic of Germany for use in human subjects. Temozolomide is currently licensed for treating subjects with recurrent disease and since 2006 in newly diagnosed glioblastoma together with radiotherapy. The time allotted for the individual treatment sections is 6 weeks for radiotherapy, while chemotherapy will be continued until progression or unacceptable adverse effects occur. The precise chemotherapy sequence is shown in the protocol. The criteria for withdrawal from the study are defined in the protocol. Four years is the period scheduled for recruiting all patients.

Organizational Data

- DRKS-ID: DRKS00003684
- Date of Registration in DRKS: 2012/05/15
- Date of Registration in Partner Registry or other Primary Registry: 2011/12/24
- Investigator Sponsored/Initiated Trial (IST/IIT): yes
- Ethics Approval/Approval of the Ethics Committee: [---]*
- (leading) Ethics Committee Nr.: [---]*

Secondary IDs

- Primary Registry-ID: NCT01502241 (ClinicalTrials.gov)
- Sponsor-ID: NOA-08 (University of Heidelberg)
- Other Secondary-ID: 05-01

Health condition or Problem studied

- Free text: Glioblastoma
- Free text: Anaplastic Astrocytoma
- ICD10: C71 - Malignant neoplasm of brain

Interventions/Observational Groups

- Arm 1: Drug: Temozolomide
- Arm 2: Radiation: Radiotherapy of the partial brain.
Characteristics

- Study Type: Interventional
- Study Type Non-Interventional: [---]*
- Allocation: Randomized controlled trial
- Blinding: [---]*
- Control: Active control (effective treatment of control group)
- Purpose: Treatment
- Assignment: Crossover
- Phase: III
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): [---]*

Primary Outcome

- Overall survival; time frame: 12 months; The primary endpoint was overall survival, measured in days from surgery to death for any reason. Patients alive at the day of the last contact were censored.

Secondary Outcome

- Event-free survival; time frame: 12 months; Secondary efficacy end points included EFS. EFS was defined as time from surgery to first progression for patients with progression respectively to death for patients without progression. Patients without progression or death were censored at the day of the last contact. Univariate analysis of OS and EFS used Kaplan-Meier estimates21 and a Cox proportional hazard model for evaluating Hazard Ratios (HR) with 95%-confidence intervals and median OS and EFS with 95%-confidence intervals (CI).
- Best response; time frame: Within the first 8 months after surgery; Response is assessed according MacDonald Criteria based on regular 3-monthly MRI.
- Molecular prognostic or predictive biomarkers; time frame: At 12 months; Tumor tissue, fresh or paraffine-embedded, or DNA/RNA/proteins from tissue are analyzed for the status of known molecular parameters, e.g. MGMT, for a prognostic or predictive role. Further, newly discovered molecular parameters are assessed for their potential to predict outcome.

Countries of recruitment

- DE Germany
- CH Switzerland

Locations of Recruitment
Recruitment

- Planned/Actual: [--]*
- (Anticipated or Actual) Date of First Enrollment: 2005/01/31
- Target Sample Size: 412
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **65 Years**
- Maximum Age: **no maximum age**
**Inclusion Criteria**

- Histologically confirmed supratentorial anaplastic astrocytoma or glioblastoma
  - Age > 65
  - Karnofsky performance score > 60%
  - Neutrophilic granulocyte count > 1500/µl
  - Platelet count > 100,000/µl
  - Hemoglobin > 10 g/dl
  - Serum creatinine < 1.5 times the lab’s upper normal limit
  - AST or ALT < 3 times the lab’s upper normal limit
  - Alkaline phosphatase < 3 times the lab’s upper normal limit
  - No previous systemic chemotherapy
  - No previous radiotherapy to the brain
  - Written consent

**Exclusion Criteria**

- Serious medical or neurological condition with a poor prognosis
  - HIV infection
  - Second cancer requiring radiotherapy or chemotherapy (contact the study coordinator if necessary)
  - Hypersensitivity to temozolomide
  - Conditions associated with regular vomiting that might affect oral administration of the drugs
  - Psychological, familial, social or geographical circumstances with major implications for compliance with the study visit schedule
  - Patient was taking part in other intervention studies within a month of starting this study

**Addresses**
Primary Sponsor

University of Heidelberg

Telephone: [---]*
Fax: [---]*
E-mail: [---]*
URL: [---]*

Contact for Scientific Queries

University of Zurich
Michael Weller

Telephone: [---]*
Fax: [---]*
E-mail: [---]*
URL: [---]*

Contact for Public Queries

University of Zurich
Michael Weller

Telephone: [---]*
Fax: [---]*
E-mail: [---]*
URL: [---]*

Sources of Monetary or Material Support

Private sponsorship (foundations, study societies, etc.)

Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

Telephone: [---]*
Fax: [---]*
E-mail: [---]*
URL: [---]*

Status

Recruitment Status: Recruiting complete, follow-up complete
Study Closing (LPLV): 2011/11/01

Trial Publications, Results and other documents
The parameters in ClinicalTrials.gov and DRKS are not identical. Therefore the data import from ClinicalTrials.gov required adjustments. For full details please see the DRKS FAQs.
- Translation on version: 5
- Last processed date by ClinicalTrials.gov: 2013/10/30
* This entry means the parameter is not applicable or has not been set.
*** This entry means that data is not displayed due to insufficient data privacy clearing.