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Dose-intensified rechallenge with temozolomide, one week on one week off versus three weeks on one week off in patients with progressive or recurrent glioblastoma

Submission date
23/02/2009

Registration date
23/04/2009

Last Edited
07/02/2019

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2008-006871-60

ClinicalTrials.gov (NCT)
NCT00941460

Protocol serial number

2008-006871-60

Study information

Scientific Title
Dose-intensified rechallenge with temozolomide, one week on one week off versus three weeks on one week off in patients with progressive or recurrent glioblastoma: a prospective, multicentre, multinational, randomised, parallel-group, open, phase II trial

Acronym
Director

Study objectives
The primary objective of this study is to show the superiority of arm A (one week on temozolomide one week off) versus arm B (three weeks on temozolomide one week off) in terms of time to treatment failure.

On 05/01/2010 this record was updated to include further information on the site locations; this information can be found in the interventions section of this record under the above update date. At this time, the anticipated start date of this trial was also updated to the date of first participant recruitment. The initial anticipated start date of this trial was 16/03/2009.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The Ethics Committee of the Medical Faculty of Heidelberg (Ethikkommission der Medizinischen Fakultät Heidelberg), 18/06/2009, ref: AFmu-050/2009

Study design
Prospective multicentre multinational randomised parallel-group open phase II trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Progressive or recurrent glioblastoma

Interventions
In treatment arm A, patients will be treated with an initial dose of 120 mg/m^2 unless there was grade III or IV myelotoxicity with conventional temozolomide (5/28) previously. These patients will be started at 90 mg/m^2. Temozolomide will be given orally on days 1 - 7 and 15 - 21. The dose will be modified if necessary.

In treatment arm B, patients will start with an initial dose of 80 mg/m^2 unless there was significant myelotoxicity with conventional temozolomide (5/28) previously. These patients will be started at 60 mg/m^2. Temozolomide will be given orally on days 1 - 21. The dose will be modified if necessary.

1 year of treatment; follow-up until death or for one year.

Site location and principal investigator information added as of 05/01/2010:
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Updated 05/07/2012: the trial was stopped due to a slower than anticipated recruitment rate.

Updated 14/08/2014: the study is completed now and the publication is currently in preparation.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Temozolomide

Primary outcome(s)
Median time to treatment failure. Treatment failure is reached:
1. Upon tumour progression, measured every 8 weeks during treatment, every 3 months during follow-up
2. If treatment has to be terminated due to toxicity, measured at every contact between investigator and patient (according to protocol: weekly during first cycle, then every 4 weeks; during follow-up every 3 months)
3. If the patient dies for any reason

Key secondary outcome(s))
1. Progression-free survival (PFS), measured every 8 weeks during treatment, every 3 months during follow-up
2. Overall survival, measured every 8 weeks during treatment, every 3 months during follow-up
3. Objective responses (complete response [CR] and partial response [PR]), measured every 8 weeks during treatment, every 3 months during follow-up
4. Outcome (PFS-6, PFS, survival, best response) relative to MGMT promoter methylation in recurrent tumour, measured every 8 weeks during treatment, every 3 months during follow-up
5. Outcome relative to duration of prior treatment (e.g. number of completed 5/28 cycles after radiation therapy)
6. Outcome relative to interval from completion of prior TMZ chemotherapy treatment (less than 3 months versus greater than 3 months)
7. Toxicity including lymphocytes, CD4 T cell and regulatory T cell counts, measured every 8 weeks during treatment, every 3 months during follow-up
8. Expression of the mismatch repair genes MLH-1, MSH-2, MSH-6 and PMS2 in tumour tissue determined by immunohistochemistry
9. Changes in MGMT status in recurrent disease relative to initial tumour tissue if applicable, measured weekly during first cycle, then every 8 weeks; during follow-up every 3 months
10. Changes in MGMT activity in peripheral blood during ongoing therapy will be assessed during the first cycle at days 1, 8, 15, 22, then MGMT activity will be investigated every 8 weeks; during follow-up every 3 months
11. Quality of life determined by EORTC QoL-Brain 20 Neurotoxicity determined by MRI, measured every 8 weeks during treatment, every 3 months during follow-up
12. Neurotoxicity determined by Mini-Mental State Examination (MMSE), MRI and NeuroCogFx

neuropsychological examination, measured every 4 weeks during treatment, every 3 months during follow-up
13. Outcome relative to extent of resection (gross total resection versus resection with residual contrast-enhancing tumour versus biopsy)
14. Screening for aberrant MGMT promoter methylation in peripheral blood, measured weekly during first cycle, then every 8 weeks; during follow-up every 3 months

Completion date
16/03/2013

Eligibility

Key inclusion criteria
Current inclusion criteria as of 05/10/2011:
1. Progressive or recurrent glioblastoma documented by magnetic resonance imaging (MRI) no earlier than 180 days after first surgery for glioblastoma and no earlier than 90 days after completion of radiotherapy
2. Histological diagnosis of glioblastoma
3. Tissue available for the determination of MGMT promoter methylation in the primary tumor or from the recurrent tumor of a patient undergoes a surgical procedure at recurrence prior to study entry
4. Prior treatment with temozolomide administered concomitantly with radiotherapy and at least for two cycles (5/28) as an adjuvant treatment
5. Informed consent
6. Aged 18 - 80 years, either sex
7. Karnofsky performance score greater than 50%
8. Neutrophil counts greater than 1,500/µl
9. Platelet counts greater than 100,000/µl
10. Haemoglobin greater than 10 g/dl
11. Serum creatinine less than 1.5-fold upper normal range
12. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) less than three-fold upper normal range unless attributed to anticonvulsants
13. Alkaline phosphatase less than three-fold upper normal range
14. Women with childbearing potential must have a negative serum pregnancy test less than or equal to 14 days prior to study enrolment

Added 05/10/2011:
15. Willingness to apply contraception according to local requirements (as stated in patient information)

Previous inclusion criteria:
3. Tissue available for the determination of MGMT gene promoter methylation in the recurrent tumour
All other points remained unchanged.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Progressive or recurrent glioblastoma documented by MRI earlier than 180 days after first surgery for glioblastoma and earlier than 90 days after completion of radiotherapy
2. Treatment with any chemotherapy other than temozolomide according to the schedule of the EORTC NCIC trial except that an adjuvant starting dose of 200 mg/m^2 and more than six cycles of adjuvant temozolomide are allowed
3. Prior systemic or local treatment with deoxyribonucleic acid (DNA)-damaging agents, tyrosine kinase inhibitors or anti-angiogenic agents for any cancer
4. Allergy to or other intolerability of temozolomide
5. Unable to undergo MRI
6. Past medical history of diseases with poor prognosis, e.g. severe coronary heart disease, severe diabetes, immune deficiency, residual deficits after stroke, severe mental retardation
7. Human immunodeficiency virus (HIV) infection
8. Pregnancy
9. Breast feeding
10. Treatment within in any other clinical trial parallel to the treatment phase of the current study

Date of first enrolment
23/09/2009

Date of final enrolment
16/03/2013

Locations

Countries of recruitment
Austria

Germany

Switzerland

Study participating centre
University Hospital Heidelberg
Heidelberg
Germany
69120

Sponsor information

Organisation
University Hospital Heidelberg (Universitätsklinikum Heidelberg) (Germany)

ROR
https://ror.org/013czdx64

Funder(s)

Funder type
Industry

Funder Name
Essex Pharma GmbH (Germany)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2015		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes