A phase II open-label, randomized, multi-centre comparative study of bevacizumab-based therapy in paediatric patients with newly diagnosed supratentorial, infratentorial cerebellar, or peduncular high-grade glioma.

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To evaluate the efficacy, safety, tolerability, and pharmacokinetics of bevacizumab when added to postoperative radiotherapy with concomitant and adjuvant temozolomide (TMZ) and to determine whether the addition of anti-angiogenic therapy with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON39454

Source
ToetsingOnline

Brief title
Roche Herby BO 25041

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Childeren with newly diagnosed brain-tumor

Research involving

Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: bevacizumab, newly diagnosed highgrade glioma (HGG), paediatric patients, phase 2

Outcome measures

Primary outcome

Event (disease)-Free Survival (EFS) as assessed by the central radiology review

committee

Secondary outcome

1. Overall Survival (OS) and 1 year survival rate

2. 6 mongh and 1 year EFS rates

3. Event (disease)- Free Survival (EFS) as assessed by the investigates

4. Overall respoonse rate as assessed by central radiology committee

5. Functional changes in tumour on diffusion/perfusion MRI imaging

6. Health status as measured by the Health Utility Index (HUI)

7. Neuro-psychological function as measured by the Weschsler scale

8. Safety, feasibility and tolerability

Study description

Background summary

The biological rationale for the addition of the anti-angiogenic agent bevacizumab is strong for HGG in both children and adults in these highly

vascularised and VEGFRexpressing tumours. Results in adult recurrent glioblastoma have been encouraging and have led to ongoing large randomised Phase III trials in newly diagnosed patients, where it is hoped that, in addition to direct anti-angiogenic effects, there will also be a potential synergistic/additive effect with chemotherapy and radiation. In the post*human-genome era, it may be hoped that the understanding of the inherent biology of paediatric CNS tumours will lead, not only to improved therapies, but also to safer treatments and improved quality of life. This may occur through better classification, stratification/prognostication, and prediction through use of molecular markers in association with conventional therapies, as well as by defining molecular targets for new anti-cancer treatments.

Study objective

To evaluate the efficacy, safety, tolerability, and pharmacokinetics of bevacizumab when added to postoperative radiotherapy with concomitant and adjuvant temozolomide (TMZ) and to determine whether the addition of anti-angiogenic therapy with bevacizumab to the initial management of paediatric patients with newly diagnosed supratentorial, infratenrorial cerebellar, or penducular high-grade glioma (HGG) confers a clinical benefit.

The additional cohort for young patients has been added to the current study with the aim of exploring pharmacokinetics, safety, and response to bevacizumab when added to temozolomide in younger children aged 6 months to 3 years with HGG relapsing or progressing after their first-line chemo-surgical treatment

Study design

Newly diagnosed patients:
Children between the age of 3 and 18 years with a newly diagnosed histologically documented localised supratentorial, infratenrorial cerebellar, or penducular non-brainstem WHO Grade III or IV HGG are potentially eligible to participate in this study. Eligibility will, however, require the confirmation of the institution*s histopathologic diagnosis by an independent designated reference neuro-pathologist. Since the primary interest in this trial is to identify patients who have developed a tumour progression or recurrence, both patients with measurable and assessable HGG will be potentially eligible to participate in this study.

Patients with a histological confirmed WHO grade III or IV HGG diagnosis, fulfilling all the other inclusion and exclusion criteria, will be randomly assigned, using minimisation methods, to one of the following 2 treatment arms:

Arm A: Chemoradiation with TMZ followed, after a TMZ treatment break of approximately 4 weeks, by up to 12 cycles of TMZ

Arm B: Bevacizumab delivered concomitantly with Chemoradiation with TMZ, during the TMZ treatment break of approximately 4 weeks and thereafter concomitantly with 12 cycles of adjuvant TMZ

Follow-up:
On completion of study treatment, patients in whom efficacy endpoint events have not been observed must be followed for efficacy and safety.

The end of the study will be the date of the final scheduled clinic visit for the last patient to complete the study or the date on which the last data point from the last patient, which is required for the overall survival analysis has been received, whichever is the later date.
For an individual patient the end of the study (i.e. the last visit) will occur when the patient withdraws consent, has been lost to follow-up, dies or when the IDMC recommends to stopping the trial earlier than initially assumed for futility or safety issues.

Patients with progressive or relapsed disease:
Young patients aged >= 6 months to < 3 years with localised or metastatic, supratentorial, infratentoriaal cerebellair of pedunculair non-brainstem WHO Grade III or IV HGG recurring or progressing after first-line therapy with surgery and chemotherapy will receive up to twelve 28-day cycles of TMZ and bevacizumab.
This is an open-label, single-arm study of the addition of bevacizumab to TMZ given in twelve 28-day cycles:
• Bevacizumab: 10 mg/kg/every 2 weeks at Days 1 and 15
• TMZ: 150-200 mg/m2/day from Days 1-5

During the follow-up period, patients must at a minimum be monitored for the development of tumour recurrence and progression (please refer to table of follow-up assessments on page 191 of the protocol).
Once a patient has been diagnosed with either a new progressive or recurrent disease, that
patient must continue to be followed for safety only.

The approximate length of the study will be 6 years from first patient in to end of study.

Intervention

Newly diagnosed patients:
Arm A: Chemoradiation with TMZ followed, after a TMZ treatment break of approximately 4 weeks, by up to 12 cycles of TMZ
Arm B: Bevacizumab delivered concomitantly with Chemoradiation with TMZ, during the TMZ treatment break of approximately 4 weeks and thereafter concomitantly with 12 cycles of adjuvant TMZ

Patients with progressive or relapsed disease:
Twelve 28-day cycles (without radiation therapy):
• Bevacizumab: 10 mg/kg/every 2 weeks at Days 1 and 15
• TMZ: 150-200 mg/m2/day from Days 1-5

Study burden and risks

All patients experience risks from the standard treatment of Chemoradiation therapy and TMZ. This includes the known risks that come with Imaging and Laboratory Assessments.

The patients who are randomized to receive treatment with bevacizumab have an increased risk of experiencing side-effects. As bevacizumab has not been given to many children as yet there may be unknown side-effects that appear during this study.

The most important symptoms are:
- allergy and possible infusion reactions (symptoms that start within a few minutes or hours of the infusion, e.g., wheezing, tightness in the throat or chest, rash, and facial swelling)
- bleeding and high fever (this last symptom may be a sign of a serious infection associated with an impaired immune system)
- impaired brain function (e.g., dizziness, blurred vision, confusion)

(please see Investigator Brochure for all risks related with the Investigational Product)

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Newly diagnosed patients:
1. Written informed consent obtained from the patient/parents or legally acceptable representative;
2. Age at randomization: 3 to 18 years;
3. Newly diagnosed localized, supratentorial or infratentorial cerebelar or peduncular, non-brain stem WHO Grade III or IV glioma;
4. Local histological diagnosis confirmed by a designated central reference neuropathologist;
5. Availability of a baseline MRI performed according to imaging guidelines
6. Able to commence trial treatment not before 4 weeks after the neurosurgical intervention and no later than 6 weeks following the last major surgery;
7-15: Adequate bone marrow, coagulation, liver, renal function.;Patients with progressive or relapsed disease:
1. Written informed consent obtained from parents or legal representative
2. Age at enrolment: from >= 6 months to < 3 years of age
3. Progressive or relapsed metastatic or localised, supratentorial,infratentorial cerebelar or peduncular, non-brain stem WHO Grade III or IV glioma (local pathology confirmation made either at
initial diagnosis or at relapse)
4. Availability of a baseline magnetic resonance imaging (MRI) performed according to imaging guidelines
5-13 Adequate bone marrow, coagulation, liver, renal function.

Exclusion criteria

Newly diagnosed patients:
1. Metastatic (HGG) defined as evidence of neuraxis dessimination by MRI or positive CSF

cytology; Diagnostic CSF cytology is not required. If, however, CSF is obtained and the cytology proves positive, the patient would be considered to have metastatic disease and would, therefore, be ineligible
2. WHO-defined Gliomatosis cerebri (multifocal HGG);
3. Any disease or condition that contraindicates the use of the study medication/treatment or places the patient at an unacceptable risk of experiencing treatment-related complications;
4. Low probability of protocol compliance (and any specific contraindication to MRI [e.g., cardiac pacemaker, cochlear implant])
5. Radiological evidence of surgically related intracranial bleeding;
6. Prior diagnosis of a malignancy and disease-free for 5 years;
7. Prior systemic anti-cancer therapy;
8. Previous cranial irradiation.;Patients with progressive or relapsed disease:
1. WHO-defined Gliomatosis cerebri (multifocal HGG)
2. Newly diagnosed HGG below the age of 3 years
3. Relapsed HGG below the age of 6 months or above the age of 3 years regardless of the age at first onset
4. Indication for concomitant cranial irradiation, regardless of age
5. Any disease or condition that contraindicates the use of the study medication/treatment or places the child at an unacceptable risk of experiencing treatment-related complications
6. Low probability of protocol compliance (any specific contraindication to MRI [e.g., cardiac pacemaker, cochlear implant])
7. Radiological evidence of surgically related intracranial bleeding (excluding asymptomatic, resolving haemorrhagic changes associated with recent surgery and the presence of punctuate haemorrhage in the tumour)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-12-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	bevacizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-09-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2012
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-022189-28-NL
ClinicalTrials.gov	NCT01390948
CCMO	NL36252.078.11