Bevacizumab versus bevacizumab plus lomustine versus lomustine in recurrent glioblastoma.

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON27373

Bron
Nationaal Trial Register

Verkorte titel
LWNO 0901

Aandoening

recurrent glioblastoma;
bevacizumab; lomustine

Ondersteuning

Primaire sponsor: Erasmus MC - Daniel den Hoed
Prof. Dr. M.J. van den Bent, MD PhD Neuro-Oncologist
Drs. W. Taal, MD Neuro-Oncologist
Overige ondersteuning: - The Dutch Cancer Foundation ('KWF - Kankerbestrijding')
www.kwf-kankerbestrijding.nl;
- Roche Netherlands

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

9 month overall survival (9 mo OS).

Toelichting onderzoek

Achtergrond van het onderzoek

Bevacizumab is currently registered in the US for use in recurrent glioblastoma. However, its effectiveness and the best use in this tumor type has bot been established, nor is it clear if this drug should be combined with other cytotoxic drugs to improve activity. This randomized phase II trial will explore the activity of bevacizumab and of bevacizumab with lomustine in recurrent glioblastoma. The primary endpoint is 9 months overall survival, with several progression free and overall survival measures as a secondary endpoint. Quality of life studies are incorporated to establish the clinical significance of so-called pseudo-responses that have been described in bevacizumab treated patients. Translational research studies are aiming to identify early responders.

Doel van het onderzoek

The following hypothesis will be made:

1. P0 is the largest OS probability at 9 months which, if true, implies that the therapeutic activity of that regimen is too low. In the present trial, P0 has been taken as 35%;

2. P1 is the lowest OS probability at 9 months which, if true, implies that the therapeuticactivity of Bevacizumab-Lomustine combination is adequate. In the present trial, P1 has been taken as 55%;

3. α is the probability of accepting adequate activity of a drug with a true success rate equal to or lower than P0. In the present trial, α has been taken as 0.10;

4. β is the probability of rejecting adequate activity of a drug with a true success rate at least equal to P1. In the present trial, β has been taken as 0.10.

Under those hypotheses, based on a 1:1:1 randomization, the total sample size will be 44 eligible patients in each treatment arm, for a total of 132 eligible patients. A decision rule for

activity will be performed amongst the 44 eligible patients enrolled in the each of the 3 treatment arms:

1. If ≤ 19 patients still alive at 9 months out of 44 are observed, the conclusion will be that the specific treatment arm should not be further investigated;

2. If ≥ 20 patients still alive at 9 months are observed, we will conclude that the specific treatment arm warrants further investigation.

No formal test of comparison between the three treatment arms will be performed.

Onderzoeksopzet

1. 9 months OS;

2. Median PFS, PFS6, PFS12, OS6, OS12 and median OS, objective response rates and median duration of objective response;

3. Overall and progression free survival will be measured from the day of randomization;

4. End of study occurs when all of the following criteria have been satisfied:

A. The trial is mature for the analysis of the primary endpoint;

B. The database has been fully cleaned and locked for this analysis.

Onderzoeksproduct en/of interventie

Treatment with Bevacizumab (Avastin) versus Bevacizumab and Lomustine versus Lomustine.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Age ≥ 18 years;

2. WHO Performance status 0 - 2;

3. Histologically or biopsy proven glioblastoma multiforme including patients with anaplastic oligoastrocytomas with necrosis (which meets WHO 2007 criteria for glioblastoma;

4. First relapse after prior treatment with combined chemo-irradiation with temozolomide;

5. Patient may have undergone surgery for the recurrence. If operated, residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence. In case of operation, post-operative MRI must be made within 48 hours following surgery. Minimum interval of at least 4 weeks between surgery and the start of Bevacizumab treatment, and patients should have fully recovered from the surgery;

6. For non operated patients, recurrent disease must be at least one bidimensionally measurable target lesion (contrast enhancing lesion) with one diameter of at least 2cm, based on MRI scan done within two weeks prior to start of treatment;

7. Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan;

8. No prior treatment with Lomustine or other nitrosourea’s;

9. No prior treatment with Bevacizumab or other VEGF-R signalling inhibitors;

10. No radiotherapy within the three months prior to the diagnosis of progression;

11. No chemotherapy in the past four weeks;

12. No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven;

13. Normal hematological functions: neutrophils ≥ 1.5 x 109 cells/l, platelets ≥100 x 109 cells/l, Hb ≥ 6.2 mmol/l;

14. Normal liver function: bilirubin < 1.5 x upper limit of the normal range (ULN), alkaline phosphatase and transaminases (ASAT/ALAT) < 2.5 x ULN, INR < 1.5;

15. Normal renal function:

A. Calculated (Cockcroft-Gault) or measured creatinine clearance > 30 mL/min;

B. Urine dipstick for proteinuria < 2+. Patients with >□2+ proteinuria on dipstick urinalysis at baseline should undergo 24 hours urine collection and must demonstrate ≤1 g of protein/24 hr.

16. Women of reproductive potential, female patients within one year of entering the menopause as well as males must agree to use an effective non-hormonal method of contraception during the treatment period and for at least 6 months after the last dose of Bevacizumab;

17. No other diseases, interfering with follow up;

18. No geographical, psychological or other non-medical conditions interfering with follow-up;

19. Written informed consent.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. History or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding;

2. Arterial or venous thrombosis ≤ 12 months prior to registration;

3. History of myocardial infarction (≤ 6 months prior to inclusion), unstable angina, New York Heart Association (NYHA) Grade II or greater congestive heart failure, or serious cardiac arrhythmia requiring medication;

4. Uncontrolled hypertension defined by a systolic pressure > 150 mm Hg and/or diastolic

pressure > 100 mm Hg, with or without anti-hypertensive medication. Patients with initial blood pressure elevation are eligible if initiation or adjustment of anti-hypertensive medication lowers pressure to meet the entry criteria;

5. Current or recent (within 10 days of first dose of Bevacizumab) use of aspirin (> 325 mg/day) or other NSAID with anti-platelet activity or treatment with dipyramidole, ticlopidine, clopidogrel and cilostaz;

6. Use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic (as opposed to prophylactic) purposes;

7. Clinically serious (as judged by the investigator) non-healing wounds, active skin ulcers or incompletely healed bone fracture;

8. History of active gastroduodenal ulcer(s);

9. History of abdominal fistula as well as non-GI fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to inclusion;

10. Evidence of any active infection requiring hospitalization or antibiotics, within 2 weeks prior to day 1 of cycle 1;

11. Invasive procedures (major surgical procedure, open biopsy or significant traumatic injury) within 4 weeks prior to randomization, or anticipation of the need for major surgery during the course of the study treatment. Placement of a vascular access device is not considered as a major surgical procedure if performed more than 24 hours prior to Bevacizumab administration;

12. Current or recent (within 4 weeks of enrollment) treatment with another investigational drug or participation in another investigational study;

13. Known hypersensitivity to any part of the Bevacizumab formulation;

14. Hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibody;

15. Pregnant or lactating females. Serum pregnancy test to be assessed within 7 days prior to randomization;

16. Previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma in situ of the cervix and non-melanoma skin cancer.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	09-01-2009
Aantal proefpersonen:	144
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	27-07-2009
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1819

Register	ID
NTR-old	NTR1929
Ander register	EudraCT : 2009-12186-63
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A