Phase III trial exploring the combination of bevacizumab and lomustine in patients with first recurrence of a glioblastoma

Published: 07-06-2011
Last updated: 29-04-2024

Assessment whether the addition of bevacizumab to lomustine improves overall survival in patients with recurrent glioblastoma

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

Summary

ID

NL-OMON39944

Source
ToetsingOnline

Brief title
EORTC 26101

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
GBM, glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC;ondersteuning door

Roche,Hoffmann-La Roche

Intervention

Keyword: bevacizumab, glioblastoma, lomustine, recurrent

Outcome measures

Primary outcome

Overall survival

Secondary outcome

Median progression free survival (PFS), PFS6, PFS12, median OS, OS 9, OS 12,

OS24, best overall response distribution, objective and complete response rates

and median duration of objective or complete response; quality of life and

neurocognitive function, steorid use; pattern of relapse

Study description

Background summary

Despite the recently improved treatment of glioblastoma patients due to the introduction of combined chemo-irradiation with temozolomide, the prognosis of glioblastoma patients remains dismal with approximately 25% of patients still alive two years after first surgery. Once a glioblastoma recurs after initial treatment, treatment options are limited and of limited effectivity. Recurrent glioblastoma are therefore a clinically unmet need. From US clinical investigations relatively favorable results have been reported from treatment with bevacizumab, a anti-angiogenic agent, alone or in combination with CPT11 (a cytostoxic drug). Bevacizumab is a humanized monoclonal antibody against circulating Vascular Endothelial Growth Factor (VEGF). In many tumors including glioblastoma there is a significant upregulation of signalling through VEGF pathways, with significant angiogenesis. This is blocked by bevacizumab. Treatment of recurrent glioblastoma with bevacizumab resulted in up to 40% of patients still free from progression 6 month after the start of treatment. Nonetheless, the interpretation of these results is still subject to controversy, it is unclear if these endpoint are relevant for trials on recurrent glioblastome with anti-VEGF drugs. Also, the combination of bevacizumab with CPT11 is far from logical: CPT11 does not have meaningful

single agent activity in recurrent glioblastoma, increases toxicity, and many anti-epileptic drugs used in glioblastoma patients induce the metabolism of CPT11. Lomustine (CCNU,a nitrosourea) however does have single activity in glioblastoma, and is considered standard of care in recurrent glioblastoma.
The Dutch BELOB randomized phase II study was designed to establish whether the addition of bevacizumab to lomustine is of sufficient interest to warrant a full phase III study. That appears indeed to be the case. The primary endpoint of this 148 patient study was overall survival at 9 months. The 9-months overall survival was 59% in patients treated with the combination lomustine/bevacizumab, as opposed to 43% in lomustine single agent treated patients and 38% in bevacizumab single agent treated patients. Also, there are no safety concerns of this combination. The treatment in the combination arm was well tolerated, similar to the toxicity profile in the lomustine single agent arm in which a higher dosage lomustine was deployed. A full phase III study investigating whether the addition of bevacizumab to lomustine is therefore urgently indicated.

Study objective

Assessment whether the addition of bevacizumab to lomustine improves overall survival in patients with recurrent glioblastoma

Study design

Randomized phase III, 2:1 randomization, treatmentarms: arm a) the combination bevacizumab with lomustine; and arm b) control arm with single agent lomustine

Intervention

Arm a: Lomustine 90 mg/m² every 6 weeks (cap. 160 mg) + bevacizumab 10 mg/kg every 2 weeks. until progression
Arm b (control arm): Lomustine single agent 110 mg/m² every 6 weeks until progression.

Study burden and risks

Most of the burden and risk of this study is comparable to the burden and risks of treatment of which patients with a recurrent glioblastoma are exposed, with potentially toxic drugs and regular monitoring including imaging. The most significant addltional burden are the every other week intravenous administration of bevacizumab, which takes between 30 and 90 minutes. In addition to that there are the possible side-effects of treatment with bevacizumab and CCNU. Of note, the Dutch BELOB study did not show evidence of a clinically significant increase in toxicity of the combination bevacizumab and

lomustine compared to lomustine single agent.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age >= 18 years
• WHO Performance status 0 - 2
• Availability of biological material (tumor) for central review processes and translational research
projects (tumor and blood)
• Histologically or biopsy proven glioblastoma multiforme
• Unequivocal first recurrence after prior treatment with radiotherapy with concurrent and/or adjuvant temozolomide
• 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. Surgery should be completed for at least
4 weeks and patients should have fully recovered.
• For non operated patients, recurrent disease must be at least one bidimensionally measurable target lesion
(contrast enhancing lesion) with diameters of at least 1cm.
• Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan.
• No prior treatment with bevacizumab or other VEGF signalling inhibitors
• No radiotherapy within the three months prior to the diagnosis of progression
• No chemotherapy in the past four weeks (or 6 weeks in case of nitrosourea*s)
• No non tumor related surgery or other 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.
• No core biopsy or other minor surgical procedure within 7 days prior to randomization. Placement of a central vascular access device (CVAD) if performed at least 2 days prior to study treatment administration is allowed
• No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is
histologally proven
• Normal hematological functions: neutrophils >= 1.5 x 109 cells/l, platelets >=100 x 109 cells/l, Hb > 6.2 mmmol/l
• 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
• Normal renal function: calculated or measured creatinine clearance < 30 mL/min; 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. .
• 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.
• For premenopausal women: negative pregancy test, not lactating.
• No other diseases, interfering with follow up.
• No geographical, psychological or other non-medical conditions interfering with follow-up
• Written informed consent.

Exclusion criteria

• History or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding.
• Arterial or venous thrombosis <= 6 nths prior to registration

• evidence of recent hemorrhage on MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving hemorrhagic changes related to surgery, and presence of punctate hemorrhage in the tumor are permitted entry into the study
• 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.
• 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.
• significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
• prior history of hypertensive crisis or hypertensive encephalopathy
• history of pulmonary haemorrhage/haemoptysis >= grade 2 according to the NCI-CTCAE version 4.0 criteria within 1 month prior to randomization
• 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.
• International normalized ratio (INR) > 1.5 ULN and activated partial thromboplastin time (aPTT) > 1.5 × the ULN. Use of full-dose anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the atient has been on a stable dose of anticoagulants for at least two weeks before randomization. s per ASCO guidelines, LMWH should be the preferred approach.
• Clinically serious (as judged by the investigator) non-healing wounds, active skin ulcers or incompletely healed
bone fracture.
• History of active gastroduodenal ulcer(s).
• History of abdominal fistula as well as non-GI fistula, gastrointestinal perforation or intra-abdominal abscess
within 6 months prior to inclusion.
• History of intracranial abscess within 6 months prior to randomization
• Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization
• Evidence of any active infection requiring hospitalization or antibiotics, within 2 weeks prior to day 1 of cycle 1.
• Current or recent (within 4 weeks of enrollment) treatment with another investigational drug.
• Known hypersensitivity to any excipients of Bevacizumab formulation.
• Hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibody.

Study design

Design

Study phase:	3
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):	11-11-2011
Enrollment:	155
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	07-06-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-08-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-09-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-02-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	09-03-2017
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	EUCTR2010-023218-30-NL
ClinicalTrials.gov	NCT01290939
CCMO	NL36562.078.11