A Phase III, Randomised, Parallel Group, Multi-Centre Study in Recurrent Glioblastoma Subjects to Compare the Efficacy of AZD2171 [RECENTIN] Monotherapy and the Combination of AZD2171 with Lomustine to the Efficacy of Lomustine Alone

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

Summary

ID

NL-OMON31263

Source
ToetsingOnline

Brief title
D8480C00055

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Malignant brain tumour; Brain Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Farmaceutisch bedrijf: Astra Zeneca

Intervention

Keyword: Brain tumour, Glioblastoma, Malignant, VEGF

Outcome measures

Primary outcome

Progression Free Survival (PFS) as assessed by independent radiographic,

central review.

For subjects with measurable disease at entry (at least one lesion that has a

shortest diameter * 10 mm at baseline), PFS will be defined as the earliest

time that:

The sum of the products of the largest perpendicular diameters of contrast

enhancement for all lesions has increased by 25% in comparison to the nadir

scan as long as the shortest diameter is * 15 mm. If the dose of steroids has

been reduced in the 10 days prior to the scan being conducted, progression will

be based on a follow-up scan performed after the dose of steroids has been

stabilised for 10 days

The subject has died from any cause,

A new lesion is detected that is outside the original tumour volume and has a

shortest diameter * 10mm.

For subjects without measurable disease at entry (no lesions with a shortest

diameter * 10 mm at baseline), PFS will be defined as the earliest time that:

The subject has died from any cause

A new lesion is detected that is outside the original tumour volume and has a

shortest diameter * 10mm

A small enhancing lesion at baseline (*10 mm shortest diameter) has a

significant increase in size to shortest diameter * 15 mm.

Secondary outcome

Overall Survival (OS)

Radiographic Response Rate (RR)

Alive and Progression Free rate at 6 months (APF6) defined as 24 weeks, after

randomisation

Average daily steroid dosage change from baseline until progression and average

number of progression/steroid free days.

Time to deterioration of neurological status

Study description

Background summary

Currently available clinical data suggest there is increased tumour control with increasing doses of AZD2171. In Study D8480C00001, AZD2171 was biologically active at doses of 20 mg and above in terms of reduction in tumour blood flow and permeability, blood pressure increases, and reductions in sVEGFR-2 and tumour size. The MTD of AZD2171 in Study D8480C00001 was 45 mg, and this is the dose currently being used in the glioblastoma Phase II study. In the Phase II glioblastoma study conducted by Massachusetts General Hospital, preliminary data show only one subject has withdrawn due to toxicity. Ten of 16 subjects had a dose reduction and 11 of 16 required a dose interruption, but tolerability was manageable. In light of these data, the 45 mg dose of AZD2171 has been selected for further evaluation in the monotherapy arm of the study.

Study objective

The Primary Objective of the study is to dettermine the relative efficacy of AZD2171 [RECENTIN] (both monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of progression free survival (PFS) as assessed by independent radiographic radiological review.

Study design

This is a phase III, randomised, parallel group, multi-center study in subjects with recurrent glioblastoma. Subjects will be randomised to receive either AZD2171 monotherapy, AZD2171 in combination with lomustine, or lomustine with placebo. Subjects will be randomised in a 2:2:1 ratio, with the fewest subjects being randomised to the lomustine with placebo arm.

The AZD2171 monotherapy arm will be open label but the two arms containing lomustine will be double-blinded.

Intervention

Petients will receive, depending on randomization:
*AZD2171-monotherapie: a daily dose of 45 mg in two tablets of resp. 30 mg and 15 mg, both taken orally.
*Combination AZD2171/ lomustine: lomustine as one oral dose of 130mg/m2 per 6 weeks and once daily AZD2171 in a tablet of 30 mg, taken orally.
*Lomustine plus placebo: lomustine as one oral dose of 130mg/m2 per six weeks and once daily a placebo for AZD2171 in a tablet, taken orally.

If the patient does not tolerate the dose of 45mg AZD2171, lower doses may be allowable (45 mg * 30 mg * 20 mg).
For patients in the groups AZD2171/lomustine or placebo/lomustine lower doses may be alowable for AZD2171 or placebo (30 mg * 20 mg * 15 mg).

Study burden and risks

Physical examination (5x); urine samples (8x); questionnaires (7x, EORTC, BN20, EQ-5D); Vital Signs (14x); ECG (4x); Karnofski Performance Status (8x); MRI (7x); Pulmonary function once per 6 months and at discontinuation.
A total of 181.5 mL blood samples is being taken in 24 weeks.

Currently available clinical data suggest there is increased tumour control with increasing doses of AZD2171. Since angiogenesis is necessary for the growth and metastasis of all solid tumours and VEGF is believed to have a pivotal role in this process, AZD2171 treatment may have broad-spectrum clinical utility.

It is expected that the treatments in this study will be in good balance with the benefits the patient can expect, directly or through the results of the

study.

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

1. Provision of informed consent
2. Age *18 years
3. Life expectancy * 12 weeks
4. Histological/cytological confirmation of glioblastoma
5. Subjects with measurable disease (contrast-enhancing tumour *10 mm by shortest diameter) by MRI imaging within 4 weeks prior to enrolment (Visit 1). Or subjects who have undergone a resection without measurable disease prior to enrolment.
6. Subjects must have been on no steroids or a stable dose of steroids for at least 5 days before the baseline MRI (Visit 2)

7. Subjects must have received only one prior chemotherapy regimen and this regimen must contain temozolomide
8. Subjects must have a Karnofsky Performance Score of 60 or above
9. Subjects must have a mini-mental status examination score of 15 or greater

Exclusion criteria

1. Subjects on enzyme-inducing anti-epileptic drugs within 2 weeks prior to randomisation.
- Note: Subjects are eligible if they switched to non-enzyme inducing agents and discontinued enzyme-inducing agents for more than or equal to 2 weeks prior to randomisation.
2. Inadequate bone marrow reserve as demonstrated by leukocytes * 4.0 x 10 power 9 /L, an absolute neutrophil count *1.5 x 10 power 9 /L or platelet count *100 x 10 power 9 /L or requiring regular blood transfusions to maintain haemoglobin >9g/dL
3. Serum bilirubin * 1.5 x ULRR
4. ALT or AST * 2.5 x ULRR. If liver metastases are present, ALT or AST > 5x ULRR.
5. Serum creatinine > 1.5 x ULRR or a creatinine clearance of * 50mL/min calculated by Cockcroft-Gault
6. Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart unless urinary protein < 1.5g in a 24 hr period
7. History of significant gastrointestinal impairment, as judged by the Investigator, that would significantly affect the absorption of AZD2171, including the ability to swallow the tablet whole
8. Subject with a history of poorly controlled hypertension with resting blood pressure > 150/100mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy
9. Any evidence of severe or uncontrolled diseases (eg, unstable or uncompensated respiratory, cardiac, hepatic or renal disease)
10. Unresolved toxicity > CTCAE grade 1 from previous anti-cancer therapy (including radiotherapy) except alopecia (if applicable)
11. Mean QTc with Bazetts correction >470msec in screening ECG or history of familial, long QT syndrome
12. Significant haemorrhage (>30mL bleeding/episode in previous 3 months) or haemoptysis (>5mL fresh blood in previous 4 weeks)
13. Recent (<4 weeks) major surgery (including craniotomy) prior to entry into the study, or a surgical incision that is not fully healed. Subjects who have undergone brain biopsy are eligible if it has been > 2 weeks since the biopsy.
14. Pregnant or breast-feeding women or women of childbearing potential with a positive pregnancy test prior to receiving study medication
15. Known hypersensitivity to AZD2171 or any of its excipients
16. History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within 5 years, unless the subject has been disease free for 2 years and they have tissue diagnosis of the target lesion.
17. Known infection with hepatitis B or C or HIV
18. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)
19. Previous enrolment or randomisation of treatment in the present study.

20. Treatment with an investigational drug within 30 days prior to the first dose of AZD2171
21. Other concomitant anti-cancer therapy except steroids
22. Previous anti-VEGF therapy.
23. Subjects with evidence of any intratumoral or peritumoral haemorrhage deemed significant by the treating physician
24. Subjects who have received any form of cranial radiation within 3 months prior to study entry.
25. Known hypersensitivity to lomustine or any of its excipients
26. Subjects with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLCO)
27. Subjects who have progressed within 3 months of standard therapy
28. Subjects receiving radiosurgery or brachytherapy within 3 months prior to enrolment
29. Subjects on therapeutic anticoagulants (warfarin, low-molecular weight heparinoids)
30. Subjects with Celiac Disease

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2007
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	CeeNU 10 mg capsule

Generic name:	Lomustine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lomustine 40 mg capsule
Generic name:	Lomustine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Recentin tablet (15/20/30 mg)
Generic name:	Cediranib

Ethics review

Approved WMO Date:	12-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2010
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2007-000383-24-NL
CCMO	NL19608.018.07