A Randomized, Placebo Controlled Phase 3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (EGFR) Amplification (Intellance 1)

Published: 30-09-2015
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To determine whether the addition of ABT-414 to concomitant radiotherapy and temozolomide prolongs overall survival (OS) in subjects with newly diagnosed GBM harboring EGFR amplification.

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

Summary

ID

NL-OMON47442

Source
ToetsingOnline

Brief title
M13-813

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Glioblastoma, Grade 4 Brain tumor

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie B.V.

Intervention

Keyword: ABT-414, Glioblastoma Multiforme, Radiotherapy, Temozolomide

Outcome measures

Primary outcome

The primary outcome is: the overall survival (OS)

Secondary outcome

- PFS

- OS for the MGMT unmethylated group

- OS for the MGMT methylated subgroup

- OS in the sub group with EGFRvIII mutation

- PFS in the sub group with EGFRvIII mutation

- Time to deterioration in neurocognitive functioning on the Hopkins Verbal

Learning Test Revised (HVLT-R)

- Time to deterioration in symptom severity score according to M.d. Anderson

Symptom Inventory Score, Brain Tumor Module (MDASI-BT)

- Time to deterioration on symptom interference score (MDASI-BT)

- Assessment of comparative safety

Explorative endpoints are:

- OS after 1 year

- OS after 2 years

- PFS after 1 year

- PFS after 2 years

- More explorative endpoints about quality of life and neurocognitive function.

Study description

Background summary

Gliomas are the most frequent primary brain tumors in adults, with an annual incidence between 4 and 5 per 100.000 inhabitants. Glioblastomas represent 60-70% of these tumors. Glioblastomas are the most aggressive primary brain tumors in adults, with a median survival of 9 to 17 months (when treated). No curative treatment exists. Fifty to sixty percent of glioblastomas demonstrate abnormalities of the EGFR pathway: 60% show overexpression of the receptor, in 40-50% the EGFR receptor is amplified, and about 25% of the GBM population harbors a constitutively activated EGFRvIII mutation in parts of the tumor. Standard treatment consists of surgical resection to the extent safely feasible followed by radiation and concomitant and adjuvant TMZ therapy.
ABT-414 is an antibody drug conjugate (ADC) designed for the treatment of tumors expressing EGFR. ABT-414 consists of: (1) a veneered "humanized" recombinant IgG1K antibody that has binding properties specific to a unique epitope of human EGFR with (2) non-cleavable maleimido-caproyl linkers each attached to (3) a potent antimicrotubule agent, monomethylauristatin F (MMAF). The antibody binds to the activated EGFR epitope (even in the absence of the EGFRvIII mutation), is internalized, and then intracellular enzymes release the toxin leading to inhibition of microtubule function, the disruption of critical cellular processes, and cell death.
In an ongoing phase I study in GBM, ABT-414 is given intravenously (IV) every other week. This is investigated with radiotherapy and daily temozolomide (RT/TMZ) or with TMZ on day 1-5 every four weeks. In this phase I project, responses are observed in recurrent glioblastomas. Preliminary results show that 4 out of 15 recurrent glioblastoma subjects had objective responses, where these responses occurred in patients with EGFRvIII mutation or amplification. There are no preliminary results known about the effects with primary glioblastomas, because no data is present yet about recurrence of the disease. These data warrant further exploration of ABT-414 in primary GBM with EGFR amplification, in combination with radiotherapy and TMZ.

Study objective

To determine whether the addition of ABT-414 to concomitant radiotherapy and temozolomide prolongs overall survival (OS) in subjects with newly diagnosed GBM harboring EGFR amplification.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter phase 3 study.
The study consists of two arms:

Arm 1:
During the 6 week chemo radiation-phase the subject receives ABT-414 on day 1 of the 1st, 3rd and 5th week. In this period the subject receives standard radiotherapy and standard TMZ (daily dose lasting 42 days). After a recovery period of 4 weeks, the adjuvant phase will start where the subject receives TMZ during 6 cycles of 28 days on day 1-5 of every cycle and ABT-414 on day 1 and day 15 of every cycle. This will be followed by 6 cycles of 28 days where only ABT-414 on day 1 and day 15 is given.
Arm 2:
This arm is equal to the first arm, but the ABT-414 infusion will be replaced by a placebo infusion.
Amendment 3 includes an additional sub-study enrolling approximately 12 subjects with mild to moderate hepatic impairment. These subjects will receive open label ABT-414 and follow the same procedures and treatments as the blinded subjects in the blinded study.

Intervention

Chemo radiation phase:
Subjects will be treated with ABT-414, 2.0 mg/kg or Placebo, intravenous injection 30 to 40 minutes on day 1 of week 1, 3 and 5. In addition, subjects receive standard RT and TMZ (75 mg/m2) during the first 6 weeks.
Adjuvant phase:
Subjects will be treated during 12 cycles of 28 days with ABT-414, 1.25 mg/kg or Placebo, intravenous injection 30 to 40 minutes on day 1 and day 15 of every cycle. On day 1-5 of the first 6 cycles subjects will receive TMZ 150mg/m2, with the possibility to increase the dose to 200mg/m2 in subsequent cycles in case of sufficient tolerance.
The response on the treatment will be assessed by an MRI, which will be performed every 8 weeks.
The treatment stops after these 12 adjuvant cycles, but in case of a good response and tolerance of ABT-414 or placebo the treatment can be continued on request of the investigator and in negotiation with the sponsor.

Study burden and risks

The subjects participating in the study will have a higher burden because of participation in the trial. This burden consists of extra visits to the site, two times an ECG, additional blood draws besides the standard safety labs. Next to this, the subjects will complete questionnaires (among others HVLT-R and MDASI-BT) during screening, prior to the adjuvant phase and subsequently every 8 weeks. Furthermore, the subjects will be obliged to use preventive eye drops in the days surrounding ABT-414 administrations or placebo. Eye examinations will be performed during screening (1x), the chemo radiation phase (3x) and in the adjuvant phase. Furthermore an MRI will be made prior to treatment and subsequently every 8 weeks.

In Arm 1 subjects will receive an intravenous ABT-414 injection every other week. Risks in this study include toxicity from ABT-414. Next to adverse events of the standard treatment, such as TMZ and radiotherapy, ABT-414 can give adverse events. Interim safety data from a phase 1 study with ABT-414 in GBM patients show the following adverse events: Dry eyes, foreign body sensation in eyes, keratitis, photophobia, vision blurred, fatigue and headache. The current data of ABT -414 and the lack of an effective treatment alternative reflect an acceptable rationale and risk for treating adult patients with GBM with an elevated expression of EGFR with ABT -414 in the context of a clinical trial.

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. de novo GBM tumors that test positive for EGFR ampflification.
2. Age >= 18 years.
3. Karnofsky performance status >= 70 <= 14 days prior to randomization.
4. Must have recovered from effects of surgery, postoperative infection and other complications of surgery.
5. Adequate bone marrow, renal, and hepatic function <= 21 days prior to randomization.

Exclusion criteria

1. multifocal, recurrent or metastic GBM.
2. prior chemo therapy or radiosensitizer for cancer of the head and neck region.
3. prior radiotherapy to the head or neck resulting in overlap of radiation fields.
4. prior therapy for glioblastoma except surgery or other invasive malignancy.
5. prior, concomitant or planned treatment with anti-neoplastic intent including but not limited to Novo-TTF, EGFR-targeted therapy, bevacizumab, Gliadel wafers or other intratumoral or intracavity antineoplastic therapy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-05-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABT-414
Generic name:	-

Ethics review

Approved WMO Date:	30-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-11-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	01-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-06-2018
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-08-2018
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	11-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-10-2019
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	EUCTR2015-001166-26-NL
ClinicalTrials.gov	NCT02573324
CCMO	NL54003.078.15

Study results

Results posted: 24-03-2023

First publication
23-03-2023