INTELLANCE 2: ABT-414 alone or ABT-414 plus temozolomide versus lomustine or temozolomide for recurrent glioblastoma: a randomized phase II study of the EORTC Brain Tumor Group

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The objectives of the trial are to assess whether ABT-414 alone or in combination with TMZ improves overall survival (OS), PFS, tumor response, quality of life, NDFS and steroid use compared to standard treatment with lomustine single agent or TMZ...

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

Summary

ID

NL-OMON47561

Source
ToetsingOnline

Brief title
M14-483

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: Brain tumor, For pediatric sub-study: High grade glioma and DIPG, Glioblastoma

Outcome measures

Primary outcome

The primary endpoint will be OS at final analysis and Progression Free Survival

(PFS) according to RANO criteria at the interim analysis.

Pediatric sub-study - Safety including toxicities according to CTCAE criteria

(Percentage of subjects with adverse events from subject's first visit until 49

days after the subject's last dose of study drug)

Secondary outcome

Secondary endpoints will be:

* PFS according to RANO criteria and assessed by IRC and local investigators

* Objective response % (ORR)

* OS in the subgroup with EGFRvIII mutation

The following are exploratory endpoints:

* Best overall response % (BOR), complete response % (CRR), duration of

response (DR) assessed by IRC and local investigators will be computed in each

arm

* PFS in the subgroup with EGFRvIII mutation

* Neurological deterioration-free survival (NDFS)

* Steroid use

* Frequencies and percentages of Adverse Events (AEs)

* Quality of life

Pediatric sub-study

- Objective response rate, best response rate, and duration of response based

on RANO criteria

- Overall survival, Time to Progression, and Time to progression-free survival

- Changes in neurological status and functioning (including PedsQL cancer

module)

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. Glioblastoma represent 60-70% of these tumors. Glioblastomas are the most aggressive primary brain tumors in adults, with a median survival of 9 to 15 months. No curative treatment exists. Fifty to sixty percent of glioblastomas demonstrate abnormalities of the EGFR pathway: 60% show overexpression of the receptor, in 45-50% the EGFR receptor is amplified, and about half of EGFR-amplified tumors harbor 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. With the currently available treatments (TMZ, Lomustine) there is no effective treatment for recurrent glioblastoma.

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 IgG1* antibody (ABT-806) 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 glioblastoma, ABT-414 given intravenously (IV) every other week is investigated with radiotherapy and daily temozolomide (RT/TMZ) or with TMZ day 1-5 every four weeks. In this phase I project, responses have been observed in recurrent glioblastoma. Preliminary efficacy results to date showed that 4 out of 15 recurrent glioblastoma subjects had objective responses.Three of these responses occurred in patients with EGFRvIII mutation or amplification.These data warrant further exploration of ABT-414 in recurrent glioblastoma with EGFR amplification, alone and in combination with TMZ.

There is a paediatric sub-study in patients (0 to 18 years) with high grade gliomas

Study objective

The objectives of the trial are to assess whether ABT-414 alone or in combination with TMZ improves overall survival (OS), PFS, tumor response, quality of life, NDFS and steroid use compared to standard treatment with lomustine single agent or TMZ re-challenge in patients with centrally confirmed recurrent EGFR-amplified glioblastoma.

Other exploratory objectives include analyses of the sub group with EGFRvIII mutation, correlation of MGMT methylation status with clinical outcome (PFS/OS), and exploratory clinical and translational research program.

Study design

This is a randomized, open label, multicenter, phase II trial.

This study consists of three arms.
The first arm (Arm 1) will receive ABT-414 plus TMZ every 2 weeks.
The second arm (Arm 2) will receive ABT-414 monotherapy every 2 weeks.
The control arm (Arm 3) will be treated by either lomustine or TMZ depending on the timing of the relapse: (A) patients relapsing within 3 months from the end of adjuvant TMZ cycles (16 weeks from the first day of the last TMZ cycle) will receive lomustine; (B) patients relapsing three months or more after the end of TMZ chemotherapy (16 weeks from the first day of the last TMZ cycle) will receive TMZ standard dosing day 1-5 every 4 weeks.

Intervention

Patients receive one of the following treatments:
Arm 1: patients will be treated with ABT-414 1.25 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks in combination with TMZ 150 mg/m2 day 1 to 5, for the first 28-day cycle, with dose escalation to 200 mg/m2 in subsequent cycles in case of adequate tolerance. Treatment will continue until one of the treatment withdrawal criteria has been met.

Arm 2: patients will be treated with ABT-414 monotherapy 1.25 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks until one of the treatment withdrawal criteria has been met.

Arm 3: Patients in the control arm will be treated according to the timing of relapse.
Arm 3A: Patients relapsing during TMZ treatment or within the first 16 weeks after the first day of the last TMZ cycle will be treated with lomustine 110 mg/m2 on day 1 of every 42-day treatment period. Treatment will continue until one of the treatment withdrawal criteria has been met. Lomustine will be given for a maximum of one year.

Arm 3B: Patients relapsing 16 weeks or more after the first day of the last TMZ cycle will be treated with TMZ 150 mg/m2 on day 1 to 5 for the first 28-day cycle, with dose escalation to 200 mg/m2 in subsequent cycles in case of adequate tolerance. Treatment will continue until one of the treatment withdrawal criteria has been met.

Response on the treatment will be assessed by MRI every 8 weeks.

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, an ECG, additional blood draws besides the standard safety labs. Next to this the subjects will complete questionnaires and they will be obliged to use preventive eye drops in the days surrounding ABT-4141 administrations. Furthermore every 8 weeks an MRI will be performed.

In Arm 1 and 2 subjects will receive IV ABT-414 with TMZ or as monotherapy every 2 weeks.
Risks in this study include toxicity from ABT-414. Next to adverse events of the standard treatment, such as TMZ, ABT-414 monotherapy causes adverse events. Interim safety data from a phase I study of ABT-414 in Glioblastoma show the following adverse events:
Dry eye, Forein body sensation in eyes, Keratitis, Photophobia, Vision blurred, Fatigue, Headache.

The current data of ABT-4141 and the lack of an effective treatment alternative reflect an acceptable rationale and risk for treating adult patients with

cancer that has a moderate to high level of EGFR expression with ABT-414 in the context of a clinical trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed de novo (primary) Glioblastoma Multiforme with unequivocal tumor progression or recurrence.
In case of testing at the time of first progression: either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy.

2. Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule; such conditions should be assessed with the patient before registration in the trial.
3. Availability of adequate biological material (formalin-fixed paraffin embedded [FFPE] tumor) for central testing of Epithelial Growth Factor Receptor (EGFR) amplification.
4. Presence of EGFR amplification confirmed by central assessment; patients with undetermined EGFR status are excluded.
5. World Health Organization (WHO) Performance status 0 - 2.
6. No more than one line of chemotherapy for GBM (concurrent and adjuvant Temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). Chemotherapy must have been completed at least 4 weeks prior to randomization.;Pediatric sub-study:
• Subject must either have recurrent/progressive tumor or, if newly diagnosed, have completed radiation therapy at least 4 weeks prior to first dose of ABT-414.
• The investigator must confirm that the subject is able to complete the procedures required in order to assess the primary endpoints, including PK blood draws and safety assessments over the first four weeks of therapy including Day 1 of Week 5.
• The investigator believes that the potential benefit of treating the pediatric subject with ABT-414 outweighs the expected risks and that this treatment is in the best interests of the pediatric subject.
• Subjects and/or their legal guardians must be able to understand the risks and potential benefits, and grant assent/consent to participate by signing the applicable pediatric-specific informed assent and/or consent forms.
• Subject has sufficiently recovered from previous therapy.
• (For recurrent disease) No prior RT with a dose over 65Gy to the brain, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven
• No current or recent (within 4 weeks or 5 half-lives (whichever is shorter) before enrollment) treatment with another investigational drug

Exclusion criteria

1. Prior treatment with nitrosoureas.
2. Prior treatment with bevacizumab.
3. Previous exposure to Epithelial Growth Factor Receptor (EGFR) targeted agents, including EGFRvIII targeting agents and participation to placebo controlled trials on EGFR targeted agents.
4. Prior discontinuation of temozolomide chemotherapy for toxicity reasons.
5. Prior Radiation Therapy (RT) with a dose over 65 Gy in the brain, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.
6. Previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to randomization, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix.
7. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to

randomization.;Pediatric substudy:
Not allowed are subjects with known chronic liver disease and/or cirrhosis documented by the presence of one or more of the following (assessments to be performed per standard of care only if liver disease is suspected):
- Liver biopsy with histologic findings consistent with cirrhosis
- CT or US evidence of liver disease with or without portal hypertension
- Physical examination and clinical and laboratory evidence of chronic liver disease
- Colloid shift on a liver-spleen scan
- A Child-Pugh score of 6 or higher
• Female subjects of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to enrollment.
• Male subjects that are sexually active with female partner(s) of childbearing potential must agree to use an effective method of contraception from Study Day 1, during the treatment period and for at
least 6 months after the last study treatment.

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:	Completed
Start date (anticipated):	25-09-2015
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABT414
Generic name:	ABT414
Product type:	Medicine
Brand name:	Lomustine
Generic name:	Belustine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Temozolomide
Generic name:	Temodar
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2016
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:	23-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	22-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-08-2017
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:	27-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2018
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
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2019
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	EUCTR2014-004438-24-NL
CCMO	NL52590.078.15

Study results

Date completed:	24-06-2019
Results posted:	02-01-2020

First publication
20-12-2019

URL result
URL
Type

int
Naam
M2.2 Samenvatting voor de leek
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File