A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-414 for Subjects with Glioblastoma Multiforme

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The evaluation of the safety and pharmacokinetics of ABT-414 in combination with radiation plus temozolomide or temozolomide alone for subjects with Glioblastoma Multiforme.

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

Summary

ID

NL-OMON41552

Source
ToetsingOnline

Brief title
M12-356

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 objectives of Arm A include:

* Assessment of the safety of ABT-414 in combination with radiation and TMZ;

* Determination of the maximum tolerated dose (MTD) of ABT-414 in combination with radiation and TMZ;

* Determination of the Recommended Phase 2 Dose (RPTD) of ABT-414 in combination with radiation and TMZ;

* Evaluation of ABT-414 pharmacokinetic profile when used in combination with radiation and TMZ.

The primary objectives of Arm B include:

* Assessment of the safety of ABT-414 in combination with TMZ;

* Determination of the maximum tolerated dose (MTD) of ABT-414 in combination with TMZ;

* Determination of the recommended Phase 2 Dose (RPTD) of ABT-414 in combination with TMZ;

* Evaluation of ABT-414 and TMZ pharmacokinetic profiles when they are used in combination.

The primary objectives of Arm C include:

* Assessment of the safety of ABT-414 monotherapy;

* Determination of the maximum tolerated dose (MTD) of ABT-414 monotherapy;

* Determination of the recommended Phase 2 Dose (RPTD) of ABT-414;

* Evaluation of ABT-414 pharmacokinetic profiles when used in monotherapy.

The primary objectives of the Expanded Cohorts include:

* Assessment of the safety of ABT-414 at the RPTD as monotherapy or in combination with RT and TMZ.

Secondary outcome

Secondary parameters of Arm A, B and C:

* Assessment of tumor biomarkers that may correlate with efficiency, including EGFR expression by ICH, FISH and PCR.

Secondary parameter of all three the expansion cohorts is to further determine the safety of ABT-414 as monotherapy or in combination with TMZ and/or radiotherapy, in an extended population of patients.

Study description

Background summary

GBM is the most common and most aggressive type of primary brain tumor in adults, affecting 8,000 to 10,000 people per year in North America alone. Treatments may include surgical resection of the tumor, chemotherapy, radiation therapy, and immunotherapy. Despite advances in treatments, the prognosis of patients with GBM remains poor. The current standard-of-care therapy for newly diagnosed glioblastoma following surgical debulking is radiation therapy (RT) in combination with temozolomide (TMZ), followed by 6 months of further temozolomide monotherapy.

GBM tumors have unique molecular characteristics that can influence outcome and

inform treatment decisions. Phosphatase and
tensin homolog (PTEN) and EGFR expression have correlated with outcome measures. GBM tumors, particularly those with EGFR amplification, have a high rate of EGFRde2-7 mutation expression (up to 40% in the overall population and up to 60% of more in the EGFR amplification population). The presence of this mutation confers a worse prognosis.

ABT-414 is an antibody drug conjugate (ADC) designed for the treatment of tumors expressing EGFR, consisting of: 1) a veneered "humanized" recombinant IgG1* 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 EGFR epitope, is internalized, and then intracellular enzymes release the toxin leading to inhibition of microtubule function, the disruption of critical cellular
processes and cell death.

ABT-414 is expected to be a more potent and tumor-specific antibody-drug conjugate than other EGFR antibodies and will be broadly applicable to a wide variety of EGFR-expressing tumor subsets. When compared to other EGFR directed molecules, nonclinical studies to date have confirmed that ABT-414 has potency greater than what is observed with clinically available agents in a variety of human xenograft animal models, with at least an equivalent toxicity profile.

Study objective

The evaluation of the safety and pharmacokinetics of ABT-414 in combination with radiation plus temozolomide or temozolomide alone for subjects with Glioblastoma Multiforme.

Study design

Approximately 200 subjects will be enrolled at approximately 18 research sites.

The study will consist of three arms, which will be enrolled in parallel, as well as Expanded Cohorts per arm. The first arm (Arm A) will evaluate the toxicities, PK, MTD, and RPTD of ABT-414 when administered every other week in combination with standard of care radiation and temozolomide in a population of subjects with newly diagnosed GBM. The second arm (Arm B) will evaluate the toxicities, PK, MTD, and RPTD of ABT-414 when administered every other week in combination with temozolomide in a population of subjects with GBM that have either just completed adjuvant radiation and temozolomide therapy or in subjects with recurrent GBM.
The third arm (Arm C) will evaluate the toxicities, PK, MTD, and RPTD of ABT-414 when administered every other week as monotherapy in subjects with recurrent GBM.

Once the RPTD is determined, the recommended Phase 2 dose (RPTD) of ABT-414 will be evaluated in Expanded Cohorts for each respective arm. In Expanded Cohort A, approximately 12 additional subjects will be included. In expanded cohorts B and C, an additional of approximately 50 subjects will be included.

Intervention

Subjects will receive ABT-414 every other week by IV injection as monotherapy or together with the standard of care medication (Temozolomide with or without radiotherapy). Subjects can continue the use of ABT-414 progression of disease or severe adverse events.

Study burden and risks

ABT-414 is an ADC that has demonstrated robust preclinical efficacy in a broad range of tumor types, including glioblastoma cell lines that have a high degree of EGFR expression. ABT-414 also demonstrates a favorable EGFR binding ratio of tumor to normal tissue. These data together 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.

The subjects participating in the study will have a higher burden because of participation in the trial. This burden exists of extra study visits and blood draws. The subjects do not need to complete diaries or questionnaires. Other than that, the subjects will receive the standard treatment.

Contacts

Public
AbbVie B.V.

Wegalaan 9
Hoofddorp 2132 JD
NL
Scientific
AbbVie B.V.

Wegalaan 9
Hoofddorp 2132 JD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Glioblastoma Multiforme (GBM); 70 or above on Karnofsky Performance Status; adequate bone marrow function, Arm A and Expanded Cohort Arm A: Subjects with newly diagnosed GBM; Arm B: Subject has recurrent GBM measureable criteria per RANO or newly diagnosed GBM and has just completed adjuvant radiation and/or TMZ therapy; Arm C and Expanded Cohorts B and C: (With recurrent GBM) Measurable disease per RANO criteria, and have an interval of at least 12 weeks from the completion of radiation therapy to study entry OR have progression which is clearly outside the radiation field.

Exclusion criteria

For subjects in Arm A, Arm B and the Expanded Cohort with newly diagnosed GBM: Subject has received prior chemotherapy or radiotherapy for cancer in the head and neck region; Recurrent GBM in Arm B: no prior treatment bevacizumub, nitrosourea, more than 2 therapies, or has secondary GBM; Arm C and expanded cohort C with recurrent GBM: Prior treatment with bevacizumab for recurrent GBM, and secondary GBM; Allergies to temozolomide, decarbazine, IgG containing agents; Anti-cancer treatment 28 days prior to study Day 1.

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-01-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	13-02-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	07-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2015
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:	28-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2015
Application type:	Amendment
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:	18-02-2016
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:	28-09-2016
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	EUCTR2012-003884-23-NL
CCMO	NL42775.078.13