A Phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable Glioblastoma

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The primary objective of the study is to assess the anti-tumor activity for patients with GBM with a translocation or amplification in FGFR1,2,3 or 4 based on PFS.The secondary objectives of the study are to assess the anti-tumor activity for...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON44518

Source
ToetsingOnline

Brief title
Phase II study of BGJ398 in recurrent glioblastoma

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Malignant brain tumor, Primary brain tumor grade 2-4

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma B.V.
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BGJ398, FGFR alteration, Glioblastoma, Phase II study

Outcome measures

Primary outcome

The primary endpoint will be the progression-free survival rate at 6 month

(PFS6 rate) based on patients pooled from Group 1 and Group 2.

Secondary outcome

The secondary efficacy endpoints will be the ORR of patients from Group 1 and

Group 2 with radiologically assessable enhancing disease using RANO criteria

and OS.

The secondary safety endpoints will be: type, frequency, and severity of AEs

and SAEs

The secondary tolerability endpoints will be: dose interruptions, reductions

and dose intensity, and evaluations of laboratory values

Study description

Background summary

Glioblastoma (GBM) is a highly malignant brain tumor of astrocytic origin which accounts for over 50% of all gliomas. GBM has an annual incidence rate of 3 to 4 cases per 100,000 people resulting in 240,000 newly diagnosed cases worldwide each year.

The current standard treatment for GBM is surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide (TMZ). For newly diagnosed GBM, the addition of TMZ to surgery and radiation therapy prolongs median survival from 12.1 to 14.6 months and increases the five-year survival rate, from 2% to 10%. However, at recurrence, no cytotoxic or targeted

therapeutic has improved the 6-month-PFS rate of 10-20%, a median overall survival of 6-9 months, and an average 5 year overall survival of 3.3% with the possible exception of bevacizumab.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), was approved in the US for the treatment of recurrent GBM. The 6-month-PFS rate in the multiple studies ranged from approximately 29% to 50%. Despite the improvement in response provided by bevacizumab, most patients with GBM experience relapse within months and options for salvage remain extremely limited.

Genetically, GBM is characterized by complex chromosomal abnormalities. Common mutations found in GBM include: EGFR overexpression (70%); TP53, RB, INK4a, PDGF-R, VEGF-R, CMet, and HGF and PTEN. Recently it was reported that a small subset of GBMs (3.1%) harbors oncogenic chromosomal translocations that fuse in-frame the tyrosine kinase coding domains of fibroblast growth factor receptor (FGFR) genes (FGFR1 or FGFR3) to the transforming acidic coiled-coil (TACC) coding domains of TACC1 or TACC3, respectively.

Lentivectors expressing FGFR-TACC fusions injected directly into short term astrocytic cell cultures as well as the brain parenchyma of mice have been shown to fully recapitulate GBM. Subsequently FGFR-TACC induced GBM (and derived cell lines) were successfully treated with FGFR inhibitors such as BGJ398, abolishing the malignant phenotype. Finally, in-depth genomic analyses of GBM tumor samples showed that (specifically for GBM) FGFR amplification correlates tightly with the presence of FGFR-TACC translocation, suggesting that all GBM patients that harbor an FGFR amplification do so as a result of FGFR-TACC fusion.

In conclusion, FGFR-TACC fusions could potentially identify a subset of GBM patients who would benefit from targeted FGFR kinase inhibition.

Study objective

The primary objective of the study is to assess the anti-tumor activity for patients with GBM with a translocation or amplification in FGFR1,2,3 or 4 based on PFS.

The secondary objectives of the study are to assess the anti-tumor activity for patients with recurrent GBM with a translocation or amplification in FGFR1,2,3 or 4 based on ORR and OS and to characterize the safety and tolerability of BGJ398.

Study design

This is an open-label non-randomized, multicenter, phase II study of BGJ398

administered to patients with recurrent GBM, whose tumors demonstrate FGFR amplification or translocation. Patients will be enrolled in two groups, group 1 will enroll patients who are not candidates for surgery and group 2 will enroll patients who are surgical candidates.

Intervention

Group 1 will enroll patients who are not candidates for surgery. Patients in group 1 will receive 125 mg BGJ398 on a three week on, one week off schedule. Group 2 will enroll patients who are surgical candidates. Patients in group 2 will receive 125 mg BGJ398 for 5-10 days prior to surgery and will continue to receive 125 mg BGJ398 on a three week on, one week off schedule following surgery. The tumor will be evaluated for markers of FGFR pathway activation.

Study burden and risks

-Possible toxicity derived from the study treatment. The known adverse events are documented in the informed consent form (ICF).
-The study assessments are used in routine practice: venepuncture, MRI (or CT) scan, ECG. A flowchart with all assessments can be found in the ICF.
-Adequate contraception
-Frequent study visits

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)Patients with histologically confirmed GBM and/or glioma subtypes at the time of diagnosis or prior relapse.
2) Documentation of FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, FGFR2, or FGFR3.
3) RANO defined tumor progression by MRI in comparison to a prior scan
4) Patients must have received prior external beam radiotherapy and temozolomide.;Other protocol defined criteria may apply.

Exclusion criteria

1) History of another primary malignancy
2) Prior or current treatment with a FGFR inhibitor
3) Neurological symptoms related to underlying disease requiring increasing doses of corticosteroids
4) Patients must not be taking Enzyme Inducing Anti-Epileptic Drug (EIAED). If previously on an EIAED, the patient must be off of it for at least two weeks prior to study treatment.
Other protocol defined criteria may apply.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-08-2014
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	22-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2013-002200-13-NL
ClinicalTrials.gov	NCT01975701

Register	ID
CCMO	NL47351.041.13