A Phase 1b, open-label, dose-finding study of CC-90010 in combination with temozolomide with or without radiation therapy in subjects with newly diagnosed glioblastoma

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

Summary

ID

NL-OMON54644

Source
ToetsingOnline

Brief title
CC-90010-GBM-002

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Glioblastoma, Glioma

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene Corporation

Intervention

Keyword: CC-90010, Glioblastoma, Radiotherapy, Temozolomide

Outcome measures

Primary outcome

Primary Objectives

*To determine the safety and tolerability of CC-90010 in combination with TMZ

as adjuvant therapy.

*To determine the safety and tolerability of CC-90010 in combination with

TMZ+RT as concomitant therapy.

*To determine the maximum tolerated dose (MTD) and/or the recommended phase 2

dose (RP2D) of CC-90010 in combination with TMZ as adjuvant therapy.

*To determine the MTD and/or the RP2D of CC-90010 in combination with TMZ+RT as

concomitant therapy.

Secondary outcome

Secondary Objectives

*To assess the preliminary antitumor activity of the combination CC-90010+TMZ

with concomitant radiotherapy, and as adjuvant therapy in newly diagnosed GBM

subjects:

*Progression Free Survival (PFS) and PFS rate at 6- and 12- months

*Time to Progression (TTP)

*Overall survival (OS) rate at 12-months

*To characterize the pharmacokinetics (PK) of CC-90010 administered in

combination with TMZ as adjuvant therapy and with TMZ+RT as concomitant

therapy.

Study description

Background summary

CC-90010 is a new experimental drug developed by Celgene Corporation that inhibits specific proteins normally present in the body that are involved in the growth of both normal and cancerous cells. Early laboratory and animal studies showed that by inhibiting these proteins, CC-90010 can slow down and prevent the growth of cancer cells.
CC-90010 has not been approved for the treatment of cancer or any other disease and its use in this study is investigational. *Investigational* means that CC-90010 is still being studied and the investigators are trying to learn more about it.

Study objective

The current standard treatment for glioblastoma is a combination of surgery, radiation therapy (abbreviated RT), and temozolomide (abbreviated TMZ). The purpose of this study is to test the safety (any good or bad effects) of CC-90010 when combined with the standard treatment of TMZ with or without RT. The purpose is also to see if the combination of CC 90010 and TMZ with or without RT can control your disease.
Other purposes of this study are:
• To explore how long CC-90010 stays in your body when combined with TMZ with or without RT.
• To explore what effect CC-90010 and TMZ with or without RT has on biomarkers in your blood and in your cancer tissue. Biomarkers are substances (such as proteins) that can show whether the study drug is having an effect on your cancer.

The study consists of two parts; part A and B. Enrollment for Part A is closed. Part B is now globally open to enrollment and in the Netherlands upon approval by the METC.

Study design

The CC-9010-GBM-002 study is a multicenter, open-label, phase 1b, dose-escalation (Part A) and extension (Part B) study of CC-9010 in ndGBM. The

study will evaluate the addition of CC-9010 to standard treatment with TMZ as adjuvant (additional) therapy and in combination with TMZ + RT as combination therapy.
The standard of care for ndGBM includes surgical resection as far as safe to do so, followed by RT plus concomitant TMZ chemotherapy and up to 6 months of adjuvant TMZ (Stupp, 2005).

Part A dose escalation phase:
This consists of two cohorts: 1 adjuvant therapy and 2 concomitant (in Dutch called combination therapy).

1 the adjuvant therapy:
Patients received surgery for the brain tumor prior to study participation and were treated with the subsequent standard therapy consisting of TMZ and radiation (combination therapy). Then they started in this study with an additional treatment consisting of CC-9010 + TMZ (6 courses of 28 days each). In stepwise oral doses, CC-9010 has been administered in combination with TMZ to estimate the MTD and/or the RP2D of CC-9010 as adjuvant therapy. Following assessment of two dose escalation levels (or earlier as decided by the SRC) for safety and tolerability, dose escalation of the combination therapy has been initiated.

2 the combination therapy:
after brain tumor resection, patients started on a combination study therapy of CC-9010 + TMZ + radiation (5 weeks), followed by a treatment break of 4 weeks and then 6 more courses of additional treatment with CC-9010 + TMZ and after 6 courses, possibly CC-9010 alone (monotherapy)

Again, the stepwise increase of CC-9010 in combination with TMZ + RT was investigated, to estimate the MTD and/or the RP2D of CC-9010 as combination (concomitant) therapy. A Bayesian logistic regression model (BLRM) using escalation with overdose control (EWOC) (Babb, 1998; Neuenschwander, 2008) was used.

In the Netherlands, 3 patients are currently randomized who are now in monotherapy or are about to start in monotherapy. 2 of the 3 patients were randomized to the adjuvant therapy and 1 of the 3 thus in the concomitant therapy.

The current extension part (expansion phase part B) will further evaluate the safety and efficacy of CC-9010 administered at a dose of 30 mg. Two treatment groups are created: group 1 and group 2. By drawing lots it will be determined to which group the subject will be assigned. There is 67% chance the subject will be assigned to group 1 and 33% chance the subject will be assigned to group 2. Subjects in group 1 are treated with 30 mg CC-9010 in combination with TMZ+RT, then after a treatment break of 4 weeks further treated with 30 mg CC-9010 (adjuvant treatment) for up to 6 months. After that, they can be

treated with CC-9010 alone at a dose of 45 mg until progression. Subjects in group 2 receive the standard treatment consisting of TMZ+RT, followed by a treatment break of 4 weeks and then additional treatment with TMZ for up to 6 months.

All patients in part B will start immediately after tumor surgery with the combination therapy, so basically this looks like the combination therapy cohort of part A of the study. With the difference that the patients will now be split into two groups: a part that is treated with CC-9010 (group 1) and a part that is not treated with CC-9010 (group 2). In further detail:

group 1
a combination therapy of CC-9010+TMZ+RT (5 weeks), followed by a treatment break of 4 weeks and then 6 cycles of adjuvant treatment with CC-9010 + TMZ and, after 6 courses, optionally CC-9010 alone (monotherapy)

group 2
a combination therapy of TMZ+RT (5 weeks), followed by a treatment break of 4 weeks and then 6 cycles of adjuvant treatment with TMZ. This is not followed by monotherapy.

Intervention

Celgene will supply CC-90010 as formulated tablets for oral administration.
TMZ will be prescribed, sourced and administered per package insert locally as standard of care.
Study treatment may be discontinued if there is evidence of disease progression, unacceptable toxicity or subject/physician decision to withdraw.

Study burden and risks

GBM burden is essentially limited to the brain, every procedure is standard of care (surgery, RT plus TMZ).
Therefore, the burden of participation will mainly be additional procedures and expectations with regards to the study.

Contacts

Public
Celgene Corporation

ARC Uxbridge - Sanderson Road - New Denham - Buckinghamshire Sanderson Road
Uxbridge UB8 1DH
GB

Scientific
Celgene Corporation

ARC Uxbridge - Sanderson Road - New Denham - Buckinghamshire Sanderson Road
Uxbridge UB8 1DH
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Only part A
- For Adjuvant Therapy in Part A dose scalation: Subject must have recently completed standard or a hypofractionated course of radiotherapy with TMZ chemotherapy, and then have an MRI documenting stable disease prior to the first dose of CC -90010.
- For Adjuvant Therapy in Part A dose escalation:
a. All AEs resulting from prior RT+TMZ chemotherapy must have resolved to NCI CTCAE (v5.0) Grade **1 (except for laboratory parameters outlined below
b. Subject must have not experienced significant toxicity to prior RT+TMZ (i.e.,ie, Grade 4 hematological toxicity)
c. Subject must have received at least 80% of the planned standard doses of RT and/or TMZ administered throughout the 42- day concomitant period (up to 49 days).
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 in Part A.

Only part B
- For Part B randomized expansion, only subjects with primary, IDH-wild type newly diagnosed WHO Grade IV Glioblastoma will be enrolled. Prior to randomization, IDH mutation testing using sequencing must have been performed in subjects <= 55 years of age or in subjects with a history of a low grade

glioma. In subjects > 55 years of age, a negative immunohistochemistry for the IDH R132 mutation is sufficient evidence of an IDH-wild type Glioblastoma.
- For Part B randomized expansion, MGMT promoter methylation status must be available prior to randomization. This is based on evaluation of tumor tissue from surgical resection (done locally).
- Part B expansion, a post-operative baseline contrast-enhanced MRI scan must be obtained to be used for stratification of randomization. It is strongly that this scan be obtained <72 hours post-surgery (preferably within 24-48 hours post-surgery).
- Karnofsky performance status of >=70 in Part B.
- Subject must have stable or decreasing dose of steroids at least 1 week prior to start of treatment (Day 1). Dose at randomization must be <= 20 mg prednisone or <= 3 mg dexamethasone daily (or equivalent).
- Archival tumor specimens are mandatory in Part B Randomized expansion.

Inclusion Criteria for both part A and part B
- Males and females of >= 18 years of age
- Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
- Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
- Subject has newly diagnosed, histologically confirmed WHO Grade IV Glioblastoma and must have undergone complete or partial tumor resection.
- Subject must have recovered from the effects of surgery, including post-operative infections or complications.
- Prior tumor resection up to 8 weeks (preferably within 6 weeks) prior to the first dose of CC-90010.
- Subject with archival tumor tissue suitable for molecular genetic testing must give permission to access and test the tissue.
- Subject must have the normal laboratory values described on the protocol at screening.
- Females of childbearing potential (FCBP) :
o Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, one highly effective contraceptive method plus one barrier method. These measures should be used from signing the ICF, throughout the study (including dose interruptions), and for at least 6 months and 16 days following the last dose of CC 90010 and at least 180 days after the last dose of TMZ.
o Have two negative pregnancy tests as verified by the Investigator prior to starting CC-90010 and TMZ+RT or TMZ+RT:
• a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) at Screening
• a negative serum or urine pregnancy test (Investigator*s discretion) within 72 hours prior to Cycle 1 Day 1 of study treatment
o Avoid conceiving for at least 6 months and 16 days after the last dose of CC-90010 and for at least 180 days after the last dose of TMZ. The longest contraception period that is required must be followed (eg6 months and 16 days

after the last dose of study drug, instead of 180 days).
o Agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
o Females must agree to refrain from donating ova while on study treatment and for 6 months and 16 days after the last dose of CC-90010 or 180 days after the last dose of TMZ, whichever is longer.

Exclusion criteria

Applicable for Part A and Part B:
1. Prior chemotherapy or other anti-tumor treatment for GBM
2. Any known metastatic extracranial or leptomeningeal disease.
3. Secondary GBM
4. Subjects with indeterminate MGMT promoter methylation status.
5. Biopsy only of GBM at surgery, defined as < 20% resection of enhancing tumor.
6. Subject has persistent diarrhea due to a malabsorptive syndrome (such as celiac sprue or
inflammatory bowel disease) NCI CTCAE Grade >= 2, despite medical management, or any other significant GI disorder that could affect the absorption of CC-90010.
7. Subject with symptomatic or uncontrolled ulcers (gastric or duodenal), particularly those
with a history of and/or risk of perforation and GI tract hemorrhages.
8. Evidence of recent, symptomatic CNS hemorrhage on baseline MRI or CT scan and/or
CNS hemorrhage of Grade > 1 on baseline MRI scan
9. Subject who requires increasing doses of corticosteroids to treat symptomatic cerebral
edema within 14 days prior to the first dose of CC-90010.
10. Known symptomatic acute or chronic pancreatitis.
11. Impaired cardiac function or clinically significant cardiac diseases as defined in the protocol
12. Pregnant or nursing females.
13. Known HIV infection.
14. Known chronic active hepatitis B or C virus (HBV, HCV) infection
15. Subject with a requirement for ongoing treatment with therapeutic dosing of anticoagulants or for ongoing prophylactic anticoagulation.
16. History of concurrent second cancers requiring active and ongoing systemic treatment
17. Evidence of history of bleeding diathesis.
18. Subject with known prior episodes of non-arteritic anterior ischemic optic neuropathy
(NAION) should be excluded from the study.
19. Subject has any significant medical condition in the study or would place the subject at unacceptable risk if he/she were to participate in the study.

20. Subject has any condition that confounds the ability to interpret data from the study.
21. Subject with poor bone marrow reserve as assessed by Investigator such as in conditions
requiring regular hematopoietic support
22. Previous SARS-CoV-2 infection
23. Previous SARS-CoV-2 vaccine within 14 days of C1D1.

Additional exclusion criteria for Part B:
- The following therapies are not allowed:
a. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment.
b. Planned additional treatment with Tumor-treating Fields.
- Any known metastatic extracranial or leptomeningeal disease.
- Secondary GBM (ie, progression from prior low-grade or anaplastic glioma)
- Subjects with indeterminate MGMT promoter methylation status in Part B.
- Biopsy only of GBM at surgery, defined as < 20% resection of enhancing tumor.
- Evidence of recent, symptomatic CNS hemorrhage on baseline MRI or CT scan and/or CNS hemorrhage of Grade > 1 on baseline MRI scan, unless subsequently documented to have resolved.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-12-2020
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Temodal
Generic name:	Temozolomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	30-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2019-004122-25-NL
CCMO	NL72132.056.20