A Study of CC-90010 in Combination With Temozolomide With or Without Radiation Therapy in Subjects With Newly Diagnosed Glioblastoma

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04324840	RECRUITING	MARCH 27, 2020	OCTOBER 1, 2020

STUDY DESCRIPTION

Brief Summary

Study CC-90010-GBM-002 is for newly diagnosed WHO Grade IV glioblastoma to determine the safety and tolerability and evaluate escalating doses of the investigational drug CC-90010 when combined with standard of care treatment temozolomide (TMZ) with or without radiotherapy (RT). The standard of care for ndGBM includes surgical resection to the extent that is safely feasible, followed by RT plus concomitant TMZ chemotherapy, and up to 6 months of adjuvant TMZ. The study also aims to determine whether the addition of CC-90010 can control the disease.

Condition or Disease: Glioblastoma

Intervention/treatment: Drug: CC-90010
Drug: Temozolomide
Drug: CC-90010
Drug: Temozolomide

Phase: Phase 1/Phase 2

DETAILED DESCRIPTION

The dose escalation part (Part A) of the study will initially explore escalating oral doses of CC-90010 in combination with adjuvant TMZ to estimate the MTD (Maximum tolerated dose) and/or the RP2D (recommended Phase 2 Dose) of CC-90010 as adjuvant therapy. After two dose escalation levels (or earlier as decided by the Safety Review Committee) are assessed as safe and tolerated in the Adjuvant Therapy dose escalation, the Concomitant Therapy dose escalation will start, exploring escalating oral doses of CC-90010 in combination with concomitant TMZ+RT, to estimate the MTD and/or the RP2D of CC-90010 as concomitant therapy. The expansion part (Part B) will further evaluate the safety and efficacy of CC-90010 administered at or below the MTD determined for the Adjuvant Therapy and the Concomitant Therapy in Part A, in expansion cohorts of approximately 20-30 evaluable subjects each, in order to further define the RP2D. Parts A and B will consist of three periods: Screening, Treatment, and Follow-up periods.

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 126 participants

Intervention Model : Parallel Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: 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

Actual Study Start Date: July 2020

Estimated Primary Completion Date: April 2023

Estimated Study Completion Date: November 2024

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Adjuvant Treatment CC-90010-with standard dose TMZ	Drug: CC-90010 CC-90010 (eg.dose levels 15mg, 30mg, 45 mg) will be given once daily by mouth 4 days on/24 days off every 28-day cycle for 6 cycles. If subjects complete this period with no evidence of disease progression per RANO criteria, subject might receive CC-90010 as monotherapy at RP2D of 45 mg given 4 days on/24 days off in each 28-day cycle, until stopping criteria are met. Drug: Temozolomide Temozolomide Drug: CC-90010 CC-90010 (e.g., 15 mg, 30 mg and 45 mg) will be given orally once daily (4 days on/24 days off) in combination with TMZ+RT for 42 days, to evaluate the initial toxicity of the combination. Following completion of 42 days of Concomitant Therapy, subjects who are fit to continue treatment will have a 4-week break before starting adjuvant therapy with CC-90010 in combination with TMZ. Drug: Temozolomide TMZ will be given orally at the standard dose of 75 mg/m2 per day for 7 days per week from the first day of radiotherapy until the last day of radiotherapy for 42 days. Following completion of 42 days of Concomitant Therapy, subjects who are fit to continue treatment will have a 4-week break before starting adjuvant therapy.

Experimental: Concomitant treatment. CC-90010 combined with standard dose TMZ and RT	Drug: CC-90010 CC-90010 (eg.dose levels 15mg, 30mg, 45 mg) will be given once daily by mouth 4 days on/24 days off every 28-day cycle for 6 cycles. If subjects complete this period with no evidence of disease progression per RANO criteria, subject might receive CC-90010 as monotherapy at RP2D of 45 mg given 4 days on/24 days off in each 28-day cycle, until stopping criteria are met. Drug: Temozolomide Temozolomide Drug: CC-90010 CC-90010 (e.g., 15 mg, 30 mg and 45 mg) will be given orally once daily (4 days on/24 days off) in combination with TMZ+RT for 42 days, to evaluate the initial toxicity of the combination. Following completion of 42 days of Concomitant Therapy, subjects who are fit to continue treatment will have a 4-week break before starting adjuvant therapy with CC-90010 in combination with TMZ. Drug: Temozolomide TMZ will be given orally at the standard dose of 75 mg/m2 per day for 7 days per week from the first day of radiotherapy until the last day of radiotherapy for 42 days. Following completion of 42 days of Concomitant Therapy, subjects who are fit to continue treatment will have a 4-week break before starting adjuvant therapy.

OUTCOME MEASURES

Primary Outcome Measures:	1. Adverse Events (AEs) [Time Frame: Up to 5 years] An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. 2. Maximum Tolerated Dose (MTD) of CC-90010 [Time Frame: Up to 12-14 months] Is the highest dose that causes DLTs in not more than 33% of the subjects treated with CC-90010 in the first cycle with at least 6 evaluable subjects treated at this dose. 3. Recommended Phase 2 Dose (RP2D) of CC-90010 [Time Frame: Up to 12-14 months] RP2D is usually the highest dose with acceptable toxicity, it might be the MTD or one dose level below.
Secondary Outcome Measures:	1. Progression-free survival (PFS) [Time Frame: Up to 5 years] It is defined as the time from the first dose of CC-90010 to the first occurrence of disease progression or death from any cause. 2. Overall survival (OS) [Time Frame: Up to 5 years] It is measured as the time from the first dose of CC-90010 to death due to any cause and will be analyzed in a manner similar to that described for PFS. 3. Time to Progression [Time Frame: Up to 5 years] It is defined as the time from the first dose of CC-90010 until disease progression 4. Response by Response Assessment in Neuro-Oncology (RANO) criteria [Time Frame: Up to 5 years] Response should be assessed per RANO criteria. During Adjuvant Therapy, subjects will be evaluated for preliminary anti-tumor activity with MRI scan at the end of Cycle 2 and every even numbered Cycle (±7 days). During Concomitant Therapy, subjects will be initially evaluated for anti-tumor activity on Day 70 (-7 days) or at the end of week 10 (-1 week), following completion of the combination treatment of CC-90010+TMZ+RT. The Week 10 MRI scan must be interpreted before the subject can start Adjuvant Therapy 5. Pharmacokinetics- Cmax [Time Frame: Up to 2 years] Maximum observed plasma concentration 6. Pharmacokinetics- AUC [Time Frame: Up to 2 years] Area under the plasma concentration time-curve 7. Pharmacokinetics- Tmax [Time Frame: Up to 2 years] Time to maximum plasma concentration 8. Pharmacokinetics- t1/2 [Time Frame: Up to 2 years] Terminal half-life 9. Pharmacokinetics - CL/F [Time Frame: Up to 2 years] Apparent clearance 10. Pharmacokinetics - VzF [Time Frame: Up to 2 years] Apparent volume of distribution

ELIGIBILITY CRITERIA

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:
Subjects must satisfy the following criteria to be enrolled in the study criteria:
1. Males and females of ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Newly diagnosed, histologically confirmed WHO Grade IV Glioblastoma and must have undergone complete or partial tumor resection.
3. Toxicities resulting from surgery must have resolved to NCI CTCAE (v5.0) Grade ≤ 1 prior to starting CC-90010 treatment (with the exception of Grade 2 alopecia).
4. For Concomitant Therapy: Prior tumor resection up to 8 weeks prior to the first dose of CC-90010.
5. For Adjuvant Therapy: 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.
6. For Adjuvant Therapy:
1. All AEs resulting from prior RT+TMZ chemotherapy must have resolved to NCI CTCAE (v5.0) Grade 1 (except for laboratory parameters outlined below).
2. Subject must have not experienced significant toxicity to prior RT+TMZ (i.e., Grade 4 hematological toxicity)
3. 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).
7. Subject with archival tumor tissue suitable for molecular genetic testing must give permission to access and test the tissue.
8. Life expectancy of at least 3 months.
9. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1.
10. Subject must have the following laboratory values at screening:
1. Absolute neutrophil count (ANC) ≥ 1.5 x 109/L without growth factor support for 7 days (14 days if subject received pegfilgrastim).
2. Hemoglobin (Hgb) ≥10 g/dL
3. Platelet count (plt) ≥150 x 109/L
4. Serum potassium concentration within normal range, or correctable with supplements
5. Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) and serum glutamate pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) ≤ 3.0 x Upper Limit of Normal (ULN).
6. Serum total bilirubin ≤ 1.5 x ULN.
7. Serum creatinine ≤ 1.5 x ULN or measured glomerular filtration rate (GFR) ≥ 50 mL/min/1.73 m2 using an exogenous filtration marker such as iohexol, inulin, 51Cr EDTA or 1125 iothalamate, or creatinine clearance of ≥ 50 mL/min using Cockroft-Gault equation.
8. Serum albumin > 3.5 g/dL
9. PT (or INR) and APTT within normal range
11. Females of childbearing potential (FCBP) and men with partners of child bearing potential must agree to take contraceptive measures for duration of treatment and for at least 46 days after last dose of CC-90010 for females and for 106 days after last dose of CC-90010 for males, and for 180 days after last dose of Temozolomide for both males and females
12. Males must agree to refrain from donating semen while on study drug and for 106 days after discontinuation of CC-90010 or 180 days after the last dose of TMZ, whichever is longer.
13. Females must agree to refrain from donating ova while on study treatment and for 46 days after the last dose of CC-90010 or 180 days after the last dose of TMZ, whichever is longer.
Exclusion Criteria:
The presence of any of the following will exclude a subject from enrollment:
1. Prior chemotherapy or other anti-tumor treatment for GBM (either approved or investigational) except for surgery and for the Adjuvant Therapy cohort, mandatory concomitant TMZ+RT.
2. 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.
3. Subject with symptomatic or uncontrolled ulcers (gastric or duodenal), particularly those with a history of and/or risk of perforation and GI tract hemorrhages.
4. Evidence of recent, symptomatic CNS hemorrhage on baseline MRI or CT scan.
5. Subject who requires increasing doses of corticosteroids to treat symptomatic cerebral edema within 14 days prior to the first dose of CC-90010.
6. Known symptomatic acute or chronic pancreatitis.
7. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
- LVEF 480 msec (CTCAE Grade ≥ 2), using Fridericia's QT correction formula.
- A history of additional risk factors for Torsades de pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
- The use of concomitant medications that prolong the QT/QTc interval.
- Unstable angina or myocardial infarction ≤ 6 months prior to starting CC-90010.
- Other clinically significant heart disease such as congestive heart failure requiring treatment or uncontrolled hypertension (blood pressure ≥ 160/95 mm Hg).
8. Pregnant or nursing females.
9. Known HIV infection.
10. Known chronic active hepatitis B or C virus (HBV, HCV) infection.
- Subjects who are seropositive due to HBV vaccination are eligible.
- Subjects who have no active viral infection and are under adequate prophylactics against HBV re-activation are eligible.
11. Subject with a requirement for ongoing treatment with therapeutic dosing of anticoagulants (e.g., warfarin, low molecular weight heparin, Factor Xa inhibitors, thrombin antagonists), or for ongoing prophylactic anticoagulation. Low dose low molecular weight heparin for catheter maintenance is allowed.
12. History of concurrent second cancers requiring active and ongoing systemic treatment, except non-melanoma skin cancer, completely resected cervical carcinoma in situ, low risk prostate cancer (cT1-2a N0 and Gleason score ≤ 6 and PSA CTCAE Grade 2 or haemoptysis > 1 teaspoon within 4 weeks prior to the first dose of CC-90010.
14. Subject with known prior episodes of non-arteritic anterior ischemic optic neuropathy (NAION) should be excluded from the study. CC-90010 should be used with caution in subjects with retinitis pigmentosa.
15. Subject has any significant medical condition (e.g., active or uncontrolled infection, hepatic or renal disease), laboratory abnormality, or psychiatric illness that would prevent the subject from participating (or compromise compliance) in the study or would place the subject at unacceptable risk if he/she were to participate in the study.
16. Subject has any condition that confounds the ability to interpret data from the study.
17. Subject with poor bone marrow reserve as assessed by Investigator such as in conditions requiring regular hematopoietic support (blood or platelet transfusions, erythropoietin, granulocyte colony stimulating factor [GCSF] or other hematopoietic growth factors).

CONTACTS AND LOCATIONS

Contacts

Contact:

Locations

Italy	Ospedale San Raffaele	Milano
Italy	Istituto Clinico Humanitas	Milan
Italy	Azienda Ospedaliera Universitaria Integrata Verona	Verona
Netherlands	Erasmus Universitair Medisch Centrum	Rotterdam
Netherlands	University Medical Center Utrecht	Utrecht
Spain	Hospital Val d´Hebron	Barcelona
Spain	Hospital Universitario Fundacion Jimenez Diaz	Madrid
Spain	Hospital Doce de Octubre	Madrid

Sponsors and Collaborators

Celgene

Investigator

Study Director : Zariana Nikolova, MD, PhD Celgene

MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT04324840
Other Study ID Numbers :	CC-90010-GBM-002, U1111-1248-0496, 2019-004122-25
First Posted :	March 27, 2020
Last Update Posted :	October 1, 2020
Last Verified :	September 2020
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Yes
Plan Description:	Information relating to our policy on data sharing and the process for requesting data can be found at the following link: https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Supporting Materials:	Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), Clinical Study Report (CSR), Analytic Code
Time Frame:	See Plan Description
Access Criteria:	See Plan Description
URL:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No
Keywords provided by Celgene:	*CC-90010* *Temozolomide* *Glioblastoma* *NEWLY DIAGNOSED Radiation therapy* *Safety* *Tolerability* *MTD and RP2D*
Additional relevant MeSH terms :	*Glioblastoma*