A randomized, open-label, multicentric, two-arm pivotal trial of SonoCloud-9 combined with carboplatin (CBDCA) vs standard of care lomustine (CCNU) or temozolomide (TMZ) in patients undergoing planned resection for first recurrence glioblastoma

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To evaluate and compare the survival outcome of patients with first recurrence of glioblastoma undergoing surgical debulking/resection followed by either implantation of the SC9 device and repeat BBB opening in association with carboplatin...

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

Summary

ID

NL-OMON56543

Source
ToetsingOnline

Brief title
SONOBIRD

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain tumor, Glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Carthera
Source(s) of monetary or material Support: Sponsor Carthera

Intervention

Keyword: Blood-Brain Barrier, Carboplatin, Glioblastoma

Outcome measures

Primary outcome

Overall survival (OS), defined as the time from the date of randomization to the date of death due to any cause or censored at the time of last follow-up, calculated according to the Kaplan Meier method.

Secondary outcome

• Progression Free Survival (PFS)

Progression-free survival is defined as the time from randomization date to the earlier of the following events: unequivocal tumor progression as determined per RANO criteria or death due to any cause

• Frequency and severity of adverse events scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, from surgery to End-of-Trial Intervention visit

• Tumor Growth Rate

Tumor Growth Rate will be determined by measuring hyperintense tumor volume using T1w contrast-enhancing tumor-related region from post-surgery MRI baseline to unequivocal progression MRI (i.e., suspected radiologic progression

confirmed by repeat scan) or W20-22 MRI, whichever comes first

• Overall survival at 9, 12,18 and 24 months defined as rate of patients alive at 9 and 24 months (OS9, OS12; OS18, OS24)

• Response rate (in patients with evaluable disease, per RANO criteria)

• Rate of patients who are progression-free at 3, 6 and 6 months (PFS3, PFS6, PFS9)

• Patient Reported Outcome will be assessed using the EQ-5D-5L, the EORTC QLQ-C30, and the EORTC QLQ-BN20 quality of life questionnaires at inclusion (baseline), 6 and 12 weeks after start of treatment as well as End-of-Trial Intervention visit. Patient Reported Outcome will be collected in all patients, irrespective of treatment arm and irrespective of subsequent line therapy initiated in the meantime.

BBB opening will be evaluated by measuring post-sonication detectable ultrasound-induced gadolinium enhancement on T1w MRI at cycle 1.

• Blood levels of circulating exosomes, circulating S100B, proteins derived from the brain parenchyma, and cell-free nucleic acids.

• Tumor tissue assessment of nucleic acid derived (DNA methylation, DNA sequencing based, RNA sequencing) as well as protein related

• Correlation of level of protein-derived with disease control and PFS

• Tumor Growth Rate within and outside the field of sonication

Study description

Background summary

The brain is protected from any toxic or inflammatory molecule by the blood-brain barrier (BBB). This physical barrier is located at the level of the blood vessel walls. Because of these barrier properties, the blood vessels are also impermeable to the passage of therapeutic molecules from the blood to the brain. The development of effective treatments against glioblastoma is thus limited due to the BBB that prevents most
of drugs injected in the bloodstream from getting into brain tissue where the tumor is seated. The SonoCloud- 9 (SC9) is an investigational device using ultrasound technology and specially developed to open the BBB in the area of and surrounding the tumor. The transient opening of the BBB allows more drugs to reach the brain tumor tissue. Carboplatin is a chemotherapy that is approved to treat different cancer types alone or in
combination with other drugs, and has been used in the treatment of glioblastoma. Despite its proven efficacy in laboratory on glioblastoma cells, carboplatin does not readily cross the BBB in human. A clinical trial has shown that in combination with the SonoCloud-9, more carboplatin can reach the brain tumor tissue. The objective of the proposed trial is to show that the association -carboplatin with the SonoCloud-9- will increase
efficacy of the drug in patients with recurrent glioblastoma.

Study objective

To evaluate and compare the survival outcome of patients with first recurrence of glioblastoma undergoing surgical debulking/resection followed by either implantation of the SC9 device and repeat BBB opening in association with carboplatin chemotherapy or standard of care 2nd line chemotherapy with either lomustine or temozolomide (per best physician*s choice and best practice)

Study design

Comparative two-arm pivotal trial

Intervention

Participants in one group will be given SonoCloud-9 together with carboplatin (Experimental group) whileparticipants in the other group will be given lomustine or temozolomide (Control group). These drugs passthe BBB quite well and are marketed for treatment of glioblastoma for decades. It will be up to the doctor to choose between lomustine or temozolomide depending what he/she thinks to be the most appropriate for
the patient considering his/her disease history.

Study burden and risks

Participants may experience side effects due to the intervention either included in the Experimental or in the
Control group.
There are known side effects associated with the chemotherapy drugs (carboplatin, lomustine and temozolomide) such as decrease in blood cells, bleeding, nausea or vomiting, mouth sores, hair loss or peripheral neuropathy (sensation of pins and needles) in the hands or feet. In both group, participants will be followed by oncologists experienced with these chemotherapy drugs. Furthermore, in the Experimental group, the following side effects associated with the SonoCloud-9 -reported during previous studies- may be experienced by the participants: wound infections, temporary brain swelling (reversible accumulation of fluid in the brain), altered mental state, pain, discomfort or fainting during the
transdermal needle connection, temporary facial weakness (short loss of the ability to move one side of your face), transient dizziness, headaches, transient language disorder or blurred vision during the SonoCloud-9 activation. Most of the reported side effects are transient and manageable. There may also be unknown side effects.

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. Histologically proven glioblastoma (WHO criteria 2021), absence of IDH mutation demonstrated by negative IDH1 R132H staining on IHC. 2. Patient must have received prior first line therapy that must have contained both: a) Prior surgery or biopsy and standard fractionated radiotherapy (1.8-2 Gy/fraction, >56 Gy<66 Gy) or hypofractionated radiotherapy (15 x 2.66 Gy or similar regimen) b) One line of maintenance chemotherapy and/or immune- or biological therapy, (with or without TTFields) 3. First, unequivocal disease progression with a) measurable tumor (>100 mm2 or 1 cm3, based on RANO criteria) documented (e.g., increase of 25% in tumor diameter) on MRI performed within 14 days of inclusion and, b) interval of a minimum of 12 weeks since the completion of prior radiotherapy, unless there is a new lesion outside the radiation field or unequivocal evidence of viable tumor on histopathological sampling 4. Patient is candidate for craniotomy and at least 50% resection of enhancing region 5. Maximal enhancing tumor diameter prior to inclusion <= 5 cm on T1w. (In case of planned lobectomy, post operative peritumoral brain or residual size <=5 cm) 6. WHO performance status <= 2 (equivalent to Karnofsky Performance Status, KPS >= 70) 7. Age >= 18 years 8. Participant must be recovered from acute toxic effects (

Exclusion criteria

1. Multifocal enhancing tumor on T1w (unless all localized in a 5 cm diameter area)
2. Posterior fossa tumor
3. Known BRAF/ NTKR mutated patients
4. Patient at risk of surgery site infection (e.g., 2 or more previous craniotomies/neurosurgery within the last 3 months, poor skin condition, and/or

previously infected surgical field, or any other condition that is of increased infectious risk in the opinion of the neurosurgeon)
5. Patient treated at high, stable -or average- dose of corticosteroids (>= 6 mg/day dexamethasone or equivalent) in the 7 days prior to inclusion. Patients on dexamethasone for reasons other than mass effect may still be enrolled.
6. Contra-indication to carboplatin, CCNU or TMZ
7. Known history of hypersensitivity reactions to perflutren lipid microsphere components or to any of the inactive ingredients in ultrasound resonator
8. Patient has received bevacizumab for other reasons (such as tumor progression) than treating edema
9. Peripheral neuropathy or neuropathy >= grade 2
10. Uncontrolled epilepsy or evidence of intracranial pressure
11. Patient with known intracranial aneurism or having presented intra-tumor significant spontaneous hemorrhage
12. Patient with unremovable coils, clips, shunts, intravascular stents, and/or wafer, or reservoirs
13. Patient with medical need to be on continued anti-platelet aggregation therapy and/or anticoagulation. Patients for whom anticoagulation/platelet aggregation can be temporarily interrupted may be eligible after discussion and prior authorization by the sponsor.
14. Patient receiving enzyme-inducing antiepileptic drugs (namely phenytoin, carbamazepine and derivatives, phenobarbital), unless switched on another antiepileptic regimen
15. History of other malignancy within 3 years prior to study start with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma, non-melanomatous skin cancer or carcinoma in situ of the uterine cervix
16. Patient with known or suspected active or chronic infections
17. Patient with known significant cardiac disease, known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure > 90 mm Hg), uncontrolled systemic hypertension, or acute respiratory distress syndrome
18. Known sensitivity/allergy to gadolinium, or other intravascular contrast agents
19. Patient with impaired thermo-regulation or temperature sensation
20. Pregnant, or breastfeeding patient
21. Any other serious patient medical or psychological condition that may interfere with adequate and safe delivery of treatment and care (e.g., positive human immunodeficiency virus [HIV] status, potential blood-borne infections,*), circumstance (e.g., sinus opening during surgery), psychological, morphological characteristics (e.g., skin characteristics, bone thickness), or any pre-existing comorbidities that in the investigator*s opinion may prevent the implantation of the device, may impair the ability of the patient to receive treatment with SonoCloud-9 or may be confounding for evaluation of the clinical trial endpoints
22. Patients under guardianship, curatorship, under legal protection or deprived of liberty by an administrative or judicial decision

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-09-2024
Enrollment:	5
Type:	Actual

Medical products/devices used

Generic name:	SC9 implantation kit with SC9 transdermal needle and SC9 generator
Registration:	No

Ethics review

Approved WMO Date:	08-02-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	08-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
ClinicalTrials.gov	NCT05902169
CCMO	NL85005.000.23