A phase III trial of marizomib in combination with standard temozolomide-based radiochemotherapy versus standard temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma-MIRAGE

Published: 30-04-2018
Last updated: 10-04-2024

The primary objective of this study is to compare overall survival (OS) in patients receiving Marizomib in combination with standard treatment (TMZ with concomitant RT, followed by TMZ maintenance therapy: TMZ/RT*TMZ) with patients receiving...

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

Summary

ID

NL-OMON52595

Source
ToetsingOnline

Brief title
EORTC-1709-BTG

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym

glioblastoma / brain tumour

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Glioblastoma, Marizomib, Phase III, Temozolomide

Outcome measures

Primary outcome

The primary objective of this study is to compare overall survival in patients receiving Marizomib in combination with standard treatment (TMZ with concomitant RT, followed by TMZ maintenance therapy: TMZ/RT*TMZ) with patients receiving standard treatment only (TMZ/RT*TMZ). The testing strategy is defined to assess this objective in both the whole population and the subgroup of unmethylated MGMT patients with adequate statistical power.
The median OS is 16 months in the standard treatment alone, the median OS is 21.6 months for standard treatment plus marizomib. Lenght is FU will be accordingly.

Secondary outcome

Secondary objective is to compare PFS in the two treatment arms in the whole population.

Further secondary objectives are:

-To assess the safety and tolerability of marizomib combined with TMZ/RT*TMZ.

-To assess the neurocognitive function and quality of life of patients treated

with this approach.

-Descriptive and correlative translational research

-To evaluate pharmacokinetics in the MRZ arm

Study description

Background summary

TGlioblastoma, a grade IV glioma, is not only the most malignant but also the most common primary brain tumor in adults. The median survival of glioblastoma patients is in the range of one year in population-based studies (Gramatzki D, Dehler S, Rushing EJ, Zaugg K, Hofer S, Yonekawa Y, et al. Glioblastoma in the Canton of Zurich, Switzerland revisited: 2005 to 2009. Cancer 2016; 122(14): 2206-15) and is in the range of 15-16 months in clinical trial populations (Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014; 370(8): 709-22; Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014; 370(8): 699-708). Since 2005, patients with newly diagnosed glioblastoma aged 70 years or younger are treated with maximal safe surgery followed by involved-field radiotherapy (RT) with concomitant temozolomide (TMZ) therapy followed by up to 6 cycles of maintenance temozolomide therapy (TMZ/RT*TMZ) according to results of the EORTC 26981/22981-NCIC CE3 trial (Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352(10): 987-96; Weller M, van den Bent M, Hopkins K, Tonn JC, Stupp R, Falini A, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol 2014; 15(9): e395-403).
The proteasome is a central cellular structure for the turnover of proteins. Its activity is constituted by multiple proteases assembled in a large multi-protein complex. Cancer cells often exhibit enhanced proteasome activity and inhibition of proteasome activity may preferentially affect the viability of cancer cells, including glioblastoma cells (Wagenknecht B, Hermisson M, Eitel K, Weller M. Proteasome inhibitors induce p53/p21-independent apoptosis in human glioma cells. Cell Physiol Biochem 1999; 9(3): 117-25; Wagenknecht B, Hermisson M, Groscurth P, Liston P, Krammer PH, Weller M. Proteasome inhibitor-induced apoptosis of glioma cells involves the processing of multiple caspases and cytochrome c release. J Neurochem 2000; 75(6): 2288-97; Scoccianti S, Detti B, Gadda D, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. Radiother Oncol 2015; 114(2): 230-8).

Marizomib displays a unique pharmacologic profile among proteasome inhibitors characterized by high potency and irreversible pan-proteasome inhibition. Preclinically, marizomib has been shown to induce apoptotic cell death in stable human glioma tumor cell lines and in glioma stem cells, as well as in intracranial glioblastoma models in vivo (Manton CA, Johnson B, Singh M, Bailey CP, Bouchier-Hayes L, Chandra J. Induction of cell death by the novel proteasome inhibitor marizomib in glioblastoma in vitro and in vivo. Sci Rep 2016; 6: 18953; Di K, Lloyd GK, Abraham V, MacLaren A, Burrows FJ, Desjardins A, et al. Marizomib activity as a single agent in malignant gliomas: ability to cross the blood-brain barrier. Neuro Oncol 2016; 18(6): 840-8; Bota AA, Alexandru D, Keir ST, Bigner D, Vredenburgh J, Friedman HS. Proteasome inhibition with bortezomib induces cell death in GBM stem-like cells and temozolomide-resistant glioma cell lines, but stimulates GBM stem-like cells* VEGF production and angiogenesis. J Neurosurg 2013; 119(6): 1415-23.). Preclinical data strongly support the conclusion that marizomib is brain penetrant.
As of the data cut date of 08 Sep 2017, marizomib has been tested in 139 patients with newly diagnosed and recurrent glioblastoma in phase Ib and phase I/II studies, respectively.
Single agent MRZ activity was clearly observed but was limited: 1 confirmed PR (per RANO) lasted for 10 months and 3 additional patients had long disease stabilization lasting for 11, 8, and 8+ months. As of 08 Sep 2017, 1 of 30 patients is still on study following 9 cycles of treatment. Although the overall survival (OS) data for the study are not yet mature (16 patients censored), the median is 11.4 months, with a median follow-up for all surviving patients of 7.0 months. A phase Ib trial of marizomib in combination with standard doses and schedules of TMZ/RT*TMZ in newly diagnosed glioblastoma has been ongoing and the dose level of 0.8 mg/m2 was selected for further clinical evaluation.

Study objective

The primary objective of this study is to compare overall survival (OS) in patients receiving Marizomib in combination with standard treatment (TMZ with concomitant RT, followed by TMZ maintenance therapy: TMZ/RT*TMZ) with patients receiving standard treatment only (TMZ/RT*TMZ). The testing strategy is defined to assess this objective in both the whole population and the subgroup of unmethylated MGMT patients with adequate statistical power.

Secondary objective is to compare PFS in the two treatment arms in the whole population.
Further secondary objectives are:
- To assess the safety and tolerability of marizomib combined with TMZ/RT and TMZ.
- To assess the neurocognitive function and quality of life of patients treated with this approach.
- Descriptive and correlative translational research

-To evaluate pharmacokinetics in the MRZ arm

Study design

This is a multicenter, randomized, controlled, open label phase III superiority trial with an early stopping rule for futility.
After signing the informed consent form and upon confirmation of the patient eligibility, patients will be randomized 1:1 to the experimental arm (addition of marizomib to the standard treatment) or the standard arm.

Experimental arm: Standard radiotherapy (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m2 p.o. daily for 6 weeks (during radiotherapy) and marizomib (MRZ) dose 0.8 mg/m2 IV at days 1, 8, 15, 29 and 36.
This is followed, after 4-week break, by up to 6 cycles of maintenance TMZ 150-200 mg/m2 p.o. on days 1-5 of a 28-day cycle and up to 18 cycles of maintenance MRZ treatment (0.8 mg/m2 IV) at days 1, 8, 15 of a 28-day cycle until disease progression, unacceptable toxicity or withdrawal of consent.
Continuation of maintenance temozolomide beyond 6 cycles is not encouraged, but will not constitute a protocol violation as long as it does not exceed 12 cycles in total.

Standard arm: Standard radiotherapy (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m2 p.o. daily for 6 weeks (during radiotherapy) then (after 4-week break) up to 6 cycles of maintenance TMZ 150-200 mg/m2 p.o. on days 1-5 of a 28-day cycle.
Continuation of maintenance TMZ beyond 6 cycles is not encouraged, but will not constitute a protocol violation as long as it does not exceed 12 cycles in total.

Intervention

Experimental arm: Standard radiotherapy (RT) (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m2 p.o. daily for 6 weeks (during radiotherapy) and marizomib (MRZ) dose 0.8 mg/m2 IV at days 1, 8, 15, 29 and 36.
This is followed, after 4-week break, by up to 6 cycles of maintenance TMZ 150-200 mg/m2 p.o. on days 1-5 of a 28-day cycle and up to 18 cycles of maintenance MRZ treatment (0.8 mg/m2 IV) at days 1, 8, 15 of a 28-day cycle until disease progression, unacceptable toxicity or withdrawal of consent.
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Continuation of maintenance TMZ beyond 6 cycles is not encouraged, but will not constitute a protocol violation as long as it does not exceed 12 cycles in total.

Study burden and risks

The subjects participating in the studywill have a higher burden because of participation in the trial. This burden consists of extra visits to the site, , additional blood draws besides the standard safety labs. Next to this the subjects will complete questionnaires. Furthermore every 8 weeks an MRI will be performed.

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

Histologically confirmed newly diagnosed glioblastoma (WHO grade IV)
• Tumor resection (gross total or partial), or open biopsy only (No stereotactic biopsy)
• Availability of FFPE tumor block or 24 unstained slides for MGMT analysis
• Patient must be eligible for standard TMZ/RT*TMZ
• Karnofsky performance score (KPS) >= 70
• Recovered from effects of surgery, postoperative infection and other complications of surgery
(if any)
• The patient is at least 18 years of age on day of signing informed consent
• Stable or decreasing dose of steroids for at least 1 week prior to inclusion
• The patient has a life expectancy of at least 3 months
• Patient has undergone a brain MRI within 14 days of randomization but after intervention
(resection or biopsy)
• Women of child bearing potential (WOCBP) must have a negative urine or serum pregnancy test within 7 days prior to randomization.
• Patients of childbearing / reproductive potential must agree to use adequate birth control
measures, as defined by the investigator, during the study treatment period and for at least 6
months after the last study treatment. A highly effective method of birth control is defined as
those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly. Patients must also agree not to donate sperm during the study and for 6 months after receiving the last dose of study medication.
• Women who are breast feeding must agree to discontinue nursing prior to the first dose of study
treatment and until 6 months after the last study treatment.
• Ability to understand the requirements of the study, ability to provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the
study restrictions and return for the required assessments.
• Before patient registration/randomization, written informed consent must be given according to
ICH/GCP, and national/local regulations.

Exclusion criteria

• Patients with known IDH mutation (IDH mutation testing should be conducted for younger patients (<55 years old), for patients with tumors with atypical features and for patients with history of present concurrent lower

grade gliomas).
• Prior treatment for glioblastoma other than surgery; prior RT to brain and/or prior
chemotherapy for lower grade glioma. Placement of BCNU
wafer during surgery is not allowed
• Known hypersensitivity to the active substance or any of the excipients in the IV formulation
• History of thrombotic or hemorrhagic stroke or myocardial infarction in past 6 months
• Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia,
conduction abnormalities uncontrolled by conventional intervention, and myocardial infarction
within 6 months prior to first dose
• Concurrent severe or uncontrolled medical disease (e.g., active systemic infection, diabetes,
hypertension, coronary artery disease, psychiatric
disorder) that, in the opinion of the investigator, would compromise the safety of the patient or
compromise the ability of the patient to complete the study
• Known history of current evidence of active Hepatitis B (e.g., positive HBV surface antigen) or C (e.g., HCV RNA [qualitative] is detected).
• Known or current evidence of Human Immunodeficiency Virus (HIV) (positive HIV-1/2 antibodies)
• Prior or second invasive malignancy, except non-melanoma skin cancer, completely resected cervical carcinoma in situ, low risk prostate cancer (cT1-2a N0 and Gleason score <= 6 and PSA < 10 ng/mL), either totally resected or irradiated with curative intent (with PSA of less than or equal to 0.1 ng/mL) or under active surveillance as per ESMO guidelines. Other cancers for which the subject has completed potentially curative treatment more than 3 years prior to study entry are allowed.
• Presence of any psychological, familial, sociological or geographical condition potentially
hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

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:	Recruitment stopped
Start date (anticipated):	03-08-2018
Enrollment:	98
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	30-04-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-06-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-08-2018
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-08-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-003908-50-NL
ClinicalTrials.gov	NCT03345095
CCMO	NL64398.041.18