Study of TG02 in Elderly Newly Diagnosed or Adult Relapsed Patients with Anaplastic Astrocytoma or Glioblastoma: A Phase Ib Study (STEAM)

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- to determine the recommended phase 2 dose of TG02 in combination with radiotherapy in older patients (>65 years of age) with IDHwt glioblastoma and anaplastic astrocytoma without MGMT promoter methylation- to determine the recommended phase 2...

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

Summary

ID

NL-OMON50615

Source
ToetsingOnline

Brief title
STEAM

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
anaplastic astrocytoma IDHwt, glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)

Source(s) of monetary or material Support: Adastra Pharmaceuticals,EORTC

Intervention

Keyword: anaplastic astrocytoma, Fase 1b, glioblastoma, TG02

Outcome measures

Primary outcome

group A: determination of the maximum tolerated dose of TGO2 in combination

with radiotherapy

group B: determination of the maximum tolerated dose of TGO2 in combination

with temozolomide

Groep C: progression free survival at 6 months

Secondary outcome

voor alle groups: landmark and median overall and progression free survival;

for group A and B quality of life, for group C neurological and clinical

deterioration free survival, response rate and duration, the adverse event

profile. Pharmacokinetics of TG02 (in group C only) at various timepoints

Study description

Background summary

The prognosis of patients with IDH wild type glioblastoma or anaplastic astrocytoma is poor. The current treatment consists of combined chemo-irradiation with temozolomide, but has a modest efficacy. Moreover, the prognosis of elderly patients is in particular poor, and these patients are more prone to side effects of treatment. The effectivity of the addition of temozolomide to radiotherapy is depending on the MGMT promoter methylation status. For those reasons, elderly patients with an unmethylated MGMT promoter are often treated with radiotehrapy alone, and elderly patients with MGMT promoter methylation are frequently treated with temozolomide monotherapy. Once a IDHwt glioblastoma or anaplastic astrocytoma relapses, treatment options are

often limited to chemotherapy, with a limited response rate and duration. Thus, this disease continues to represent an unmet clinical need and novel, effective agents are urgently needed.
Abberations in Cyclin Dependand Kinases (CDK's) play a major role in many malignancies. CDK inhibitors already registered for some malignancies, including breast cancer. CDK's also play a role in glioblastoma. TGO2 is an oral CDK9, 1, 2 5 and 7 inhibitor. CDK 5 is involved in the PI3K signalling system, and in the migration of glioblastoma cells.

Study objective

- to determine the recommended phase 2 dose of TG02 in combination with radiotherapy in older patients (>65 years of age) with IDHwt glioblastoma and anaplastic astrocytoma without MGMT promoter methylation
- to determine the recommended phase 2 dose of TG02 in combination with temozolomide in older patients (>65 years of age) with IDHwt glioblastoma and anaplastic astrocytoma with MGMT promoter methylation
- to determine single agent activity of TG02 in patients with recurrent IDHwt glioblastoma and anaplastic astrocytoma without MGMT promoter methylation to determine if further stduies of this drug in this setting are justified

Study design

The study will be conducted in three groups of patients:
Group A: newly diagnosed older patients (>65 years of age) with IDHwt glioblastoma and anaplastic astrocytoma without MGMT promoter methylation: treatment with TG02 and radiotherapy 40 Gy in 15 fractions, starting dose TG02 100 mg twice weekly and escalation to 150 mg twice weekly or reduction based on monitoring of toxicity
Grpoup B: newly diagnosed older patients (>65 years of age) with IDHwt glioblastoma and anaplastic astrocytoma with MGMT promoter methylation: treatment with TG02 and standard day 1-5 every 4 weeks temozolomide, starting dose TG02 100 mg twice weekly and escalation to 150 mg twice weekly or reduction based on monitoring of toxicity
Group C: patients with first recurrence of a IDHwt glioblastoma and anaplastic astrocytoma after combined chemo-irradiation with temozolomide: treatment with TG02 monotherapy 150 mg TGO2 twice weekly.

Intervention

group A: treatment with TGO2 and radiotherapye 40 gy in 15 fractions
group B: treatment with TGO2 and temozolomide standard dag 1-5 every 4 weeks schedule
group C: treatment with TGO2 monotherapy

Study burden and risks

The patients are at risk to develop adverse events related to TGO2; and they will undergo additional study measures such as quality of life questionnaires, more frequent out patient clinic follow-up visits and more extensive drawing of blood samples.

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

Specifics for groups A and B , - Newly diagnosed glioblastoma or anaplastic astrocytoma, IDH1R132H-nonmutant by immunohistochemistry locally assessed, with FFPE tissue available for central MGMT testing (treatment allocation will be performed based on centrally assessed MGMT result)
- Tumor debulking surgery, including partial resection
- Age > 65 and considered non-eligible for combination therapy (TMZ/RT*TMZ) in

Investigator's opinion
- Brain MRI within 14 days before the first dose of TG02
- central assessment of MGMT promoter methylation , Specifics for group C , - IDH1R132H-non-mutant glioblastoma or anaplastic astrocytoma at first relapse with tissue available from first surgery
- Brain MRI at the time of progression or 14 days before the first dose of TG02 and availability of last brain MRI before progression diagnosis for upload to the EORTC Imaging Platform for post-hoc central review of progression
- Diagnosis of recurrence more than 3 months after the end of RT for firstline treatment
- Patient may have been operated for recurrence. If operated:
- surgery completed at least 2 weeks before initiation of TG02 and patients should have fully recovered as assessed by investigator.
- a post-surgery MRI made within 72 hours; , - For non-operated patients: recurrent disease must be at least one bidimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on a MRI scan done within 2 weeks prior to registration *
- Age * 18 years
- Intention to be treated with standard RT/TMZ*-- >TMZ for initial treatment and at least one dose of TMZ administered; RT alone or chemotherapy alone as initial treatment are not permitted, All groups
- Karnofsky Performance Score (KPS) of 60-100
- Recovered from effects of debulking surgery, postoperative infection and other complications of surgery (if any) (CTCAE grade 0 and 1 acceptable)
- Adequate bone marrow, renal and hepatic function within the following ranges within 7 days before the first dose of TG02:
* WBC * 3 x109/L
* ANC * 1.5x109/L
* Platelet count of * 100 x109/L independent of transfusion
* Hemoglobin * 10 g/dl or * 6.2 mmol/L
* Bilirubin * 1.5 × ULN
* ALT and AST * 2.5 × ULN
* Cockcroft*Gault calculated or measured creatinine clearance of * 30 mL/min
- Life expectancy > 8 weeks , - For men of reproductive potential and women of childbearing potential: adequate contraception
- written informed consent
- Ability to take oral medication

Exclusion criteria

REGISTRATION , Specifics for groups A and B , * prior radiotherapy with overlap of radiation fields with the planned radiotherapy in this study (Group A)
* prior therapy for glioblastoma or anaplastic astrocytoma before surgery , Specifics for group C , * discontinuation of TMZ for toxicity during first-line

treatment
* no other treatment except surgery for the treatment of the first recurrence ,
All groups
* use of enzyme-inducing anti-epileptic drugs (EI-AED) within 7 days prior to the first dose of TG02 ,
* history of ventricular arrhythmia or symptomatic conduction abnormality in past 12 months prior to registration
* congestive heart failure (New York Heart Association Class III to IV, symptomatic ischemia, uncontrolled by conventional intervention, or myocardial infarction within 6 months prior to enrollment
* prolonged QTc interval (males: > 450 ms; females: > 470 ms)
* known contraindication to imaging tracer or any product of contrast media
* MRI contraindications , * concurrent severe or uncontrolled medical disease , * known human immunodeficiency virus infection or acquired immune deficiency syndrome , * previous other malignancies, except for any previous malignancy which was treated with curative intent more than 3 years prior to enrollment, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix , * Negative serum or urine pregnancy test within 72 hours prior to the first dose for WOCBP. Nursing must be discontinued at least 1 hour before first dose.
* Known hypersensitivity to the active substance of any of the excipients in the TG02 formulation, dacabarzine and temozolomide, * Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-09-2018
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	temozolomide
Generic name:	temozolomide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TG02
Generic name:	TG02

Ethics review

Approved WMO Date:	27-02-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-10-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2017-001029-42-NL
ClinicalTrials.gov	NCT03224104
CCMO	NL64274.078.18