A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF;SELINEXOR (KPT-330) IN PATIENTS WITH RECURRENT GLIOMAS

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Primary objective:• To determine the efficacy of selinexor in adults with recurrent GBM asdetermined by the 6-months progression-free survival (6mPFS) rateSecondary objectives:• To determine the efficacy of selinexor in adults with recurrent GBM...

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

Summary

ID

NL-OMON42461

Source
ToetsingOnline

Brief title
KING (KPT-330 in Gliomas)
KCP-330-004

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Brain tumor, Glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Karyopharm Therapeutics, Inc.
Source(s) of monetary or material Support: Karyopharm Therapeutics Inc.

Intervention

Keyword: Glioma, Monotherapy, Phase 2, Selinexor

Outcome measures

Primary outcome

6-months progression-free survival (6mPFS) rate (progression of disease

defined according to the RANO criteria). Note that a window of ±14 days

will be allowed around the 6-month visit and will be applied to the

calculation of the point estimate of 6mPFS.

Secondary outcome

• Response rate according to the RANO criteria

• Median overall survival (OS)

• Median progression-free survival (PFS)

• Safety

Study description

Background summary

High-grade gliomas (HGG) are defined as World Health Organization (WHO) Grade 3 and 4
tumors of glial origin. Grade 4 tumors are called glioblastoma (GBM). With approximately 70%,
GBM is the most common type of malignant primary brain tumors. More than 14,000 cases are
newly diagnosed in adults in the United States each year.1
The prognosis of GBM is very poor. An extensive infiltration of the surrounding brain tissue limits

the accessibility in surgical resection. Aggravating the blood-brain barrier is an obstacle for many
chemotherapeutic agents. Only small and lipophilic molecules, e.g. nitrosoureas, are able to reach
their target. Furthermore, GBM is frequently refractory to cytotoxic agents. Median overall
survival (OS) from first diagnosis is about 13-18 months.

Study objective

Primary objective:

• To determine the efficacy of selinexor in adults with recurrent GBM as determined by the 6-months progression-free survival (6mPFS) rate

Secondary objectives:

• To determine the efficacy of selinexor in adults with recurrent GBM as determined by response rate according to the Response Assessment in Neuro-Oncology (RANO) criteria
• To determine the efficacy of selinexor in adults with recurrent GBM as estimated by median overall survival (OS)
• To determine the efficacy of selinexor in adults with recurrent GBM as determined by median progression-free survival (PFS)
• To evaluate safety and tolerability of selinexor

Exploratory objectives
• To evaluate preliminary evidence of efficacy of selinexor in a group of approximately 20 patients undergoing cytoreductive surgery (Arm A).
• To compare the blood/tumor ratio of selinexor for patients who were treated with 50 mg/m2 selinexor pre-operatively with the ratio for patients who were treated with 60 mg selinexor pre-operatively.
• To compare the efficacy, tolerability, and safety of selinexor (50 mg/m2) administered twice weekly (Arm B), selinexor (60 mg) administered twice weekly (Arm C), and selinexor (80 mg) administered once weekly (Arm D).
• To evaluate preliminary evidence of efficacy of selinexor in a group of approximately 20 patients with recurrent malignant gliomas other than GBM (Arm E).
• To evaluate preliminary evidence of efficacy of selinexor in a group of approximately 10 patients with recurrent GBM or AG that is refractory to antiangiogenic treatment (Arm F).
• To explore disease response as related to isocitrate dehydrogenase (IDH) mutational status and 1p/19q deletion status (Arm E).

Study design

Open label, multicenter, Phase 2 study
• Patients will be enrolled into either an exploratory Surgical Arm (Arm A) with sequential enrollment for patients who require surgery, or Medical Arm (Arm B, Arm C, Arm D, Arm E or Arm F) for patients who are not eligible for surgery. Patients in the Surgical Arm (Arm A) will receive up to 3 doses of selinexor prior to undergoing surgery, and will resume selinexor after recovery. Patients in the Medical Arm (Arms B, C, D, E, and F) will be treated with selinexor alone. Patients will be treated until progression of disease or the development of unacceptable toxicities. Patients will also be followed for survival status.

Intervention

Screening (within 14 days prior to starting the study drug):
• Physical examination - will include measuring height, weight, blood pressure, pulse, body temperature.
• Pulse oximetry
• Blood test
• Blood for biomarker analysis will be collected.
• Performance Score
• Urinalysis
• Pregnancy test
• Electrocardiogram (ECG)
• Neurological exam
• Eye exam
• Chest x-ray
• MRI scan

For every visit:
• Routine blood test
• Urinalysis
• Pulse oximetry
• ECG
• Neurological exam
• Performance score
• Vital signs
• Physical exam, including weight.

Every 8 weeks an MRI will be done.

End of treatment
• Physical exam
• Routine blood test
• Pregnancy test
• Urinalysis
• Pulse oximetry
• Electrocardiogram (ECG)

• Neurological exam

Follow-up
Every 4 weeks assessment of disease status including CT/MRI every 8 weeks

Long term follow-up
All patients will be contacted every three months after the end of the treatment in order to continue collecting information regarding the status of disease and if any other cancer treatments have started.

Study burden and risks

As part of the safety observation repeated blood draws are done to check for renal, hepatic and hematopoietic function. In addition repeated blood draws are performed for assessment of pharmacokinetic and pharmacodynamic characteristics of the study drug. These are necessary to learn more about the effects of the study drug in the patient*s body. The eye function is under regular surveillance during the study.

All other procedures performed within this study are standard of care and would also be performed if the patients would not participate in this study. However, the visits, especially within the first cycles (i.e. weekly in cylce 1-2 and biweekly in cycles 3-5) are more frequent. This allows continous monitoring of the patients condition.

Additionally the patients have to maintain a patient diary to document compliance of selinexor intake.

Side-effects in patients receiving single-agent selinexor have been generally low-grade, consistent with events observed in patients with other hematological malignancies, and responsive to standard supportive care.

In summary, the study will test a new potential class of anticancer drug in patients who are refractory to standard therapy and for whom no approved therapy is available. The study will examine the risks with continuous monitoring of safety parameters. The possible risks of the trial are judged to be acceptable and balanced with regards to the potential benefits.

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. Confirmed diagnoses, as follows:;a. Arms A, B, C, and D: Pathologically confirmed GBM (including all histologic variants) at first diagnosis with radiographic evidence of recurrent disease after treatment with radiotherapy and temozolomide;;b. Arm E: Pathologically confirmed malignant gliomas other than GBM (WHO Grade 2 or Grade 3), with radiographic evidence of recurrent disease after treatment with radiotherapy and at least one line of systemic treatment;;c. Arm F: Pathologically confirmed GBM (including all histologic variants) or AG that is refractory to antiangiogenic treatment (defined as recurrence or progression of disease per RANO criteria during prior therapy with bevacizumab or other direct VEGF/VEGFR inhibitors) with radiographic evidence of recurrent disease after treatment with radiotherapy and temozolomide; ;2. Age >= 18 years; ;3. Karnofsky Performance Status (KPS) >= 60;;4. Patients enrolling in the medical arm (Arms B,C, D, E, and F) must be on a stable or decreasing dose of corticosteroids (or none) for at least 5 days prior to the baseline MRI;;5. Patients must have received prior treatment with radiation therapy and either temozolomide (Arms A, B, C, D, and F) or at least one line of systemic treatment (Arm E).;o Patients enrolling in the medical arm (Arms B, C, D, E, and F) must have an interval of at least 12 weeks from completion of radiation therapy and study unless there is histologic proof of active tumor from intervening resection.;6. Measurable disease (according to RANO guidelines, within 14 days of starting treatment). Measurable disease after surgery on Arm A is not required.;7. Written informed consent obtained prior to any screening procedures.

Patients must be willing and able to comply with the protocol and aware of the investigational nature of this study.;8. Patients must have adequate bone marrow function and organ function within 2 weeks of study treatment as defined by the following laboratory criteria;;o Hematopoietic function: total white blood cell (WBC) count >= 3000/mm³, absolute neutrophil count (ANC) >= 1500/mm³, platelet count >= 125,000/mm³; hemoglobin >= 9g/dL.;o Hepatic function: bilirubin <= 2 times the upper limit of normal (ULN), ALT <= 2.5 times ULN, AST <= 2.5 times ULN; unless bilirubin elevation is related to Gilbert*s Syndrome for which bilirubin must be < 4 times ULN.;o Renal function: estimated creatinine clearance of >= 30 mL/min, calculated using the formula of Cockroft and Gault or other standard methods at the treating institution.;9. All female patients of childbearing potential must agree to use reliable methods of birth control during study treatment and for 3 months after the last dose of study drug and have a negative serum pregnancy test at screening. Reliable methods of contraception include intrauterine devices, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release], abstinence or sterilization of the partner.;10. Fertile males must be willing to employ reliable methods of contraception during study treatment and for 3 months after the last dose of study drug.;11. Archived paraffin-embedded tissue: approximately 10 unstained slides (if less, contact Sponsor) or a tumor block must be available for confirmation of tumor diagnosis and correlative studies.;12. Patients in the Surgical Arm (Arm A) must be predicted pre-operatively to have sufficiently sized tumor to be resected and provide tissue samples for exploratory assessments.

Exclusion criteria

1. Patients must not have significant medical illness that in the Investigator*s opinion cannot be adequately controlled with appropriate therapy or would compromise the patient*s ability to tolerate this therapy.;2. < 24 days from prior temozolomide, < 6 weeks from nitrosourea, < 4 weeks from other chemotherapy or investigational agents prior to start of treatment within study. ;3. For Arm F only: < 6 weeks from prior bevacizumab or other direct VEGF/VEGFR inhibitor prior to start of treatment within the study For any question of the definition of a direct VEGF/VEGFR inhibitor, consult Sponsor.;4. Unstable cardiovascular function.;5. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen); hepatitis testing is not required.;6. Known HIV infection; HIV testing is not required.;7. Markedly decreased visual acuity if attributed to other causes than GBM for Arms A, C, and D, malignant gliomas other than GBM (WHO Grade 2 or Grade 3) for Arm E, or GBM or AG that is refractory to antiangiogenic treatment for Arm F.;8. Active infection requiring parenteral systemic antibiotics.;9. Patients with coagulation problems and medically significant bleeding in the month prior to start of treatment (e.g., peptic ulcer, epistaxis, spontaneous bleeding). Prior history of DVT or PE is not exclusionary.;10. Patients who are pregnant or breast-feeding.;11. Other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off all therapy for that disease for a minimum of 3 years.;12. Patients must not have significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea, or inability to swallow oral medications.;13. Dehydration of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade >= 1.;14. Patients must not

have serious psychiatric or medical conditions that could interfere with treatment.;15. History of organ allograft.;16. Concurrent therapy with approved or investigational anticancer therapeutics.;17. Arms A, B, C, and D, only: Prior treatment with bevacizumab or other direct VEGF/ VEGFR inhibitors. For any question of the definition of a direct VEGF/VEGFR inhibitor, consult Sponsor.;18. Arms C and D only: body surface area < 1.2 m2, to avoid a dose exceeding the maximum allowable dose of 70 mg/m2.;.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-05-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Selinexor
Generic name:	N/A

Ethics review

Approved WMO

Date:	27-10-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	11-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2018
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	EUCTR2013-003668-30-NL
ClinicalTrials.gov	NCT01986348
CCMO	NL55009.078.15