Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication

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Primary objective* To evaluate the efficacy in terms of overall survival (OS) of erlotinib, everolimus and dasatinib in combination with radiation therapy, in patients with a DIPG both: - compared to the other experimental treatments by comparisons...

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

Summary

ID

NL-OMON49636

Source
ToetsingOnline

Brief title
BIOMEDE

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
diffuse intrinsic pontine glioma - brainstem glioma

Research involving
Human

Sponsors and support

Primary sponsor: Gustave Roussy
Source(s) of monetary or material Support: geringe bijdrage vanuit Institut Gustave Roussy en eigen fondsen

Intervention

Keyword: Biopsy, Diffuse Intrinsic Pontine Glioma, Molecular Therapy

Outcome measures

Primary outcome

The overall survival is the primary efficacy endpoint for the BIOMEDE Phase II trial.

For the comparison to historical controls, the overall survival is computed from the date of biopsy (or initial surgery). The main analysis will be based on the whole survival curve.

Secondary outcome

Efficacy endpoints

* 2-year overall survival.

The 2-year OS will be estimated from the Overall Survival curves (Kaplan Meier estimate).

* Progression-free survival

Progression-free survival from the date of biopsy/initial surgery(or date of randomisation for the comparison of randomised groups) to the date of unequivocal clinical or radiological progression, or death whatever the cause. Progression will be defined according to the RANO criteria.

* Toxicity

The safety assessment will be conducted using the NCI-CTC V4 on the whole

duration of treatment in all treatment arms, using a list of selected toxicity items for the most frequent expected adverse events and text fields for unexpected events and other less frequent toxicities. For each experimental treatment given in combination with radiotherapy, adverse events will be carefully monitored, based on the estimated proportion of patients experiencing Grade 3 / 4 CTCAE adverse event reported as a Serious Adverse Event, both in the first 8 weeks of treatment and on the whole treatment duration, excluding symptoms that are related to tumour progression or pseudoprogression (neurological deterioration, increased intracranial pressure): Each of these adverse events must be communicated directly to the trial manager team and the sponsor coordinator.

* Feasibility

- duration of treatment and description of the reasons for treatment discontinuation,
- number of treatment temporary stops and dose-reductions and the description of the reasons for these treatment modifications, and
- estimate of mean dose per week over the whole treatment duration.

* Translational study

Response to therapy (PFS and OS) will be correlated to the biomarkers identified before the start and during the course of the study (including whole exome sequencing and RNAsequencing).

* Correlation of Multimodal Imaging with Response to Therapy

The value of multimodal imaging to predict response to therapy will be evaluated.

- T1-weighted post-gadolinium imaging will be correlated with outcome since the presence of enhancement could be correlated with survival in one recent study (Hipp 2011).

- MRS: monovoxel or multivoxel proton spectroscopy will be used to assess metabolic profile especially citrate as well as Cho:Cr and Cho:NAA ratios, the latter being correlated to prognosis (Hipp 2011, Steffen-Smith 2011 & 2012).

- DCE-MRI: dynamic contrast-enhanced MRI will be used to assess perfusion since increased perfusion could predict survival (Hipp 2011); the sequences will be analysed centrally with the OLEA software.

- ASL: arterial spin-labelling perfusion MRI will be assessed as a possible surrogate for DCE-MRI. Guidelines from the "ASL Network" (http://www.asl-network.org) will be implemented.

- DWI: diffusion-weighted imaging will be used to assess the apparent diffusion coefficient as a surrogate of tumour cellularity (Gauvain 2001).

Study description

Background summary

Diffuse intrinsic poncho glioma (DIPG) is diagnosed almost exclusively in children and adolescents, with a incidence of 10 patients a year in the Netherlands. DIPG's forecast is always unfavorable; Average survival is 9 to 10 months in general and most patients die within two years after diagnosis. There is currently no validated treatment except palliative radiotherapy. The development of targeted therapies against DIPG has been limited in recent

decades due to the lack of biological data. Despite the safety of a biopsy in brain stem tumors, a biopsy was reserved only for patients with a clinically or radiologically atypical presentation, as diagnosis is made on MRI.
Reintroduction of diagnostic biopsy and molecular biological analyzes on tumor material led to new therapeutic points of action: (1) Gain / Amplification and, in particular, EGFR protein overexpression in 50% of tumors (2) Activation of the mTOR pathway through Loss of PTEN protein in 90% of patients with DIPG, often accompanied by mutations in the PI3K / AKT / mTOR pathway and (3) PDGFRA gain / amplification in 20% of tumors. These aberrations were treated with erlotinib, everolimus and dasatinib, respectively.

In 2016, the WHO classification of glioma created a new entity named *diffuse midline glioma, K27M mutant* grouping all midline gliomas with this specific histone mutation and including diffuse intrinsic pontine gliomas (Louis et al, Acta Neuropathol 2016). When treated with classical anti-glioma therapy, ie radiotherapy + temozolomide after surgery, their outcome is poor justifying new therapeutic considerations (Grill et al, J Clin Oncol 2018). Further work showed that these thalamic gliomas have a dismal prognosis similar to the DIPG (Ryall et al, Acta Neuropathol Commun 2016; Karremann et al, Neuro-Oncol 2018; Mackay et al, Cancer Cell 2018; Castel et al, Acta Neuropathologica Communications in press). Moreover, transcriptome and methylome of these diffuse midline gliomas appeared to be similar, irrespective of the location of the tumor (Castel et al, Acta Neuropathologica Communications in press). Taking into account these data, it was considered acceptable to offer these patients a treatment according to the same therapeutic paradigm than the one offered to DIPG in the BIOMEDE trial. However, there is uncertainty about their response to therapy compared to DIPG, owing for example that some of these tumours may undergo partial surgical debulking that may interfere in the evaluation of response to treatment, as well as the impact of micro-environment that may differ according to tumour site. It was thus decided not to incorporate them in the primary analysis of the trial that will be limited to children with brainstem gliomas. Patients with other midline tumours will be analysed apart and specific therapeutic modifications will be implemented in the protocol for the patients with spinal tumors who will not receive the study drug during the spinal radiotherapy.

In this study, the majority of patients received a treatment specifically aimed at the biological aberration identified in tumor biopsy. Significantly, patients were not given a drug whose protein was not present. Based on previous knowledge, this study design, by selecting patients based on presence of the point of action for medication in the tumor, was expected to increase the chance of finding a positive signal of effectiveness. By treating patients based on the expression profile of the tumor, the study aims to improve patient survival.
This study protocol is an umbrella protocol, which offers adaptive design (adaptive design) the ability to add new drugs as a research arm when available for engagement points found in DIPG tumors. Also, this design allows for

stopping ineffective arms when lacking effectiveness, and adding new research arms, according to a multi-arm multi-stage design (Sydes et al., Trials 2012, 13: 168). This flexible biomarker-driven design is a unique opportunity to quickly introduce promising new drugs into this fatal and rare disease.

An interim analysis was performed after freezing the database on Feb. 25th, 2019 after the enrollment of 230 patients {193 randomized). Based on the data provided, the IDMC recommended to stop the accrual in the randomized trial and to release the data to the study team. Indeed, "the study has reached a point of accrual where there is virtually no possibility that further enrollment on any of the arms would lead to a positive result as defined by the study protocol." The trial is therefore considered as futile since none of the arms will show its superiority with further accrual. There is however no loss of chance for the patients participating in the trial in terms of survival compared to historical controls. In addition, there is no safety signal with respect to the toxicity observed in any of the arms. Considering these information, the sponsor recommends to stop the randomization and to continue the enrollment in the arm with the best risk-benefit ratio. This would allow consolidating the data in the arm that will be considered as standard for future comparisons (i.e. BIOMEDE 2.0 that should be launched before the end of year 2019). According to the data provided, this arm would be the Everolimus arm.

Study objective

Primary objective
* To evaluate the efficacy in terms of overall survival (OS) of erlotinib, everolimus and dasatinib in combination with radiation therapy, in patients with a DIPG both:
- compared to the other experimental treatments by comparisons between randomised subsets of patients selected according to the biological abnormalities found in their tumour (pairwise direct comparisons), and
- compared to historical control

Data will continue to be acquired on the patients already randomized for the pairwise comparisons of the randomized groups, as well as the comparison to historical control. The comparison to the historical control is planned for the patients who will now be recruited in the single-arm trial.

Secondary objectives
* To compare the 2-year OS between randomised subsets of patients with DIPG (pairwise comparisons) and compared to historical controls. Data will continue to be acquired on the patients already randomized for this aspect.

* To evaluate the safety profile of each of the three drugs when administered in combination with radiotherapy, and over the whole duration of treatment, as well as the feasibility of a continuous administration of these drugs. As

everolimus may be considered as the next control arm, it is considered useful to continue to acquire data for this treatment in the meantime, first to consolidate the information about safety and efficacy in an unbiased manner and second to avoid any gap with the initiation of the second comparison in this rolling programme.

* To evaluate the efficacy in terms of progression-free survival (PFS) of erlotinib, everolimus and dasatinib in combination with radiation therapy, comparatively between randomised subsets of patients with DIPG, and also compared to historical controls. Data will continue to be acquired on the patients already randomized for this aspect.

* To evaluate the whole strategy by estimating the overall and progression-free survival of the entire cohort of patients with DIPG(by pooling the different treatment arms) and comparing it to historical controls. Data will continue to be acquired on the patients already randomized for this aspect.

* It is also considered that continuing to acquire data on nonbrainstem diffuse midline gliomas, H3K27M mutated is important to ensure these patients do not behave differently in terms of response to therapy and survival than the DIPG.

Exploratory objectives
* To study the association between known biomarkers of the targeted activation pathway (a preliminary list is given below) and response to treatment (OS, PFS) as well as to describe prospectively new tumour abnormalities that will emerge during the course of the study and evaluate their correlation with response to treatment;

* To describe the effect of therapy with morphological (MRI) and functional imaging (multimodal MRI). The rate of pseudo-progression, in particular, will be assessed since it could be as frequent as 25% (Chassot, 2011).
* To describe the outcome of the cohort of non-brainstem diffuse midline gliomas, H3K27M mutant, in terms of PFS and OS, overall and according to treatment arm, and in comparison with DIPG.

Study design

The former study was a multicenter, randomised open-label phase II trial comparing efficacy of three investigational products (i.e erlotinib, everolimus, and dasatinib). As all patients are not eligible for the three-drug comparison, the study includes three subtrials:

- R1: erlotinib versus dasatinib
- R2: everolimus versus dasatinib
- R3: erlotinib versus everolimus versus dasatinib

Eligibility criteria for the different subtrials will be based on EGFR

overexpression and PTEN loss of expression detected by immunohistochemistry. It is an adaptive design because interim efficacy analyses will be performed in the course of the trial to have the possibility of dropping one treatment arm for lack of benefit, in particular if a new experimental agent is available for testing in this disease.

Treatment allocation according to biomarker profile:
EGFR+ only: 4.25% - R1: erlotinib or dasatinib
PTEN-loss only: 38.25% - R2: everolimus or dasatinib
EGFR+ and PTEN-loss: 38.25% - R3: erlotinib, everolimus or dasatinib
None: 4.25% - Cohort dasatinib (not randomised)
Inconclusive: 15% - R3: erlotinib, everolimus or dasatinib

This expected distribution of biomarker profiles leads to the following distribution of patients per pairwise randomized comparison:
- 40% included in the direct comparison *erlotinib versus dasatinib* (Er-D comparison: 100% of R1 + 2/3 of R3 randomisations), including 30% of patients with a known EGFR positive tumour and 10% of patients with a non-informative tumour.
- 74% included in the direct comparison *everolimus versus dasatinib* (Ev-D comparison: R2 + R3 randomisations) including 64% of patients with a known PTEN-loss in the tumour and 10% of with a non-informative tumor.
- 36% included in the direct comparison *erlotinib versus everolimus* (Er-Ev comparison: R3 randomisation) including 26% of patients with a known EGFR positive + PTEN-loss tumour and 10% of with a non-informative tumor

NB: Patients with EGFR status unknown and no PTEN-loss will be eligible for the R1 randomisation. Patients with EGFR-negative and PTEN status unknown will be eligible for the R2 randomisation.

The expected distribution of treatment groups is as follows:
- 20% will receive erlotinib (50% of R1 + 33% of R3 randomization) including 15% of patients with a known EGFR positive tumor (*targeted* erlotinib cohort) and 5% of patients randomly assigned to this treatment with a non-informative tumour.
- 37% will receive everolimus (50% of R2 + 33% of R3 randomization) including 32% of patients with a known PTEN-loss in the tumor (*targeted* everolimus cohort) and 5% of patients randomly assigned to this treatment with a non-informative tumour.
- 43% will receive dasatinib (50% of R1, 50% of R2, 33% of R3 randomizations, and 100% of patients not randomised), including 8% PDGFRA+ patients. We cannot a priori define a "targeted" dasatinib cohort since we do not know which biomarker(s) defines best the tumors targeted by dasatinib.

Considering the cohort of non-brainstem diffuse midline gliomas, the distribution of the biomarkers used for randomisation is not known precisely albeit our preliminary data indicate that both biomarkers have been shown in

these tumours. These patients will not contribute to the primary analysis.

The current study will become a multicenter, open-label phase II trial evaluating Everolimus Eligibility criteria for the trial will be based on PTEN loss of expression detected by immunohistochemistry. Patients with PTEN-positivity will not be eligible for this phase 2 part evaluating Everolimus. Considering the rarity of these patients, they would only represent a handful of cases during this period of recruitment.
Considering the planned adaptive design with the possibility of dropping some treatment arms and adding new treatent arms, the
current single-arm phase 2 trial is an interim stage between the BIOMEDE-1 randomization and the future BIOMEDE-2 randomization.

Intervention

Subjects in the study will receive everolimus

Study burden and risks

It concerns children with types of cancer that are not curable. Radiotherapy and clinical as well as radiological evaluation are similar to standard care. Everolimus has shown to have a mild toxicity profile, based on the literature and the interim analysis for this study it is shown to be well tolerated by children. However, unexpected adverse events may occur.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

*Diagnosis of DIPG (clinical and radiological, or histological in case the biopsy was performed before study entry)
- Non-brainstem diffuse midline gliomas, H3K27M mutant (NB-DMG), will be eligible for the trial after biopsy or surgery. As biopsy and surgery is considered as standard practice for these locations, informed consent for the biopsy will not be necessary. Patient will sign the consent after the diagnosis to allow central review and biomarkers assessment thereafter.
*DIPG or NB-DMG at diagnosis: no prior chemotherapy for the present cancer; no prior cerebral radiation therapy
*NB : Metastatic disease allowed. Patient with metastatic disease are eligible for the study (including the randomised trial if diagnosis of DIPG/ NB-DMG confirmed). In this situation, radiotherapy will have to start within three weeks after the biopsy while targerted treatment will start at the end of the irradiation.
*Age > 6 months and < 30 years. For children below the age of 3 years, inclusion in the study and medical decisions should be discussed with the coordinating investigator.
*Eligible for a biopsy, or biopsy performed for diagnostic purpose and material available for the biomarker assessment
*Eligible for cerebral radiotherapy
*Patient covered by an health insurance if national requirement
*Written informed consent given by patient and/or parents/legal representative for biomarkers assessment and registration in the study., *Eligibility criteria for the study (see above)
*Confirmed histological diagnosis of diffuse intrinsic pontine glioma (grade II, III, IV WHO), or NB-DMG confirmed by central pathology review (including

the assessment of the loss of H3K27me3 by immunohistochemistry or the presence of a mutation in the histone H3 variant genes). Patients without classical clinical and radiological diagnostic criteria who fulfil the histological and biological criteria of DIPG are eligible for the trial. Pilocytic astrocytoma and ganglioliomas are not eligible. Patients with a suspected DIPG but no histological confirmation could be randomised if and only if the radiology is typical of a DIPG as well as the short clinical history. This would need to be reviewed and agreed centrally. Confirmation of the diagnosis of non-brainstem diffuse midline gliomas, H3K27M mutant, by central review, is needed before the randomisation of cases of NB-DMG
* PTEN-loss (evaluated by IHC). If the biomarker study is not contributive (ie no information is obtained) but the diagnosis of DIPG is ascertained either by a typical short clinical history and
typical radiological appearance or by the histology of diffuse glioma with H3K27M trimethylation loss and eventually the detection of the H3K27M mutation by immunohistochemistry, the patient will be included in the trial and will receive everolimus.
*Life expectancy > 12 weeks after the start of study treatment
*Karnofsky performance status scale or Lansky Play Scale > 50%. The PS should not take the neurologic deficit per se into account. NB: Children and young adults with a worse performance status due to glioma-related motor paresis can be included.
*Absolute neutrophil count > 1.5 x 109/l, Platelets > 100 x 109/l
*Total bilirubin < 1,5 x ULN, AST and ALT< 2,5 x ULN
*Serum creatinine < 1,5 X ULN for age. If serum creatinine > 1,5 ULN, creatinine clearance must be > 70 ml/min/1,73 m^2 (EDTA radioisotope GFR or 24 hours urines collection)
*Normal coagulation tests within the local reference ranges
*No current organ toxicity > grade 2 according to the NCI-CTCAE version 4.0 especially cardiovascular, pulmonary or renal disease (, including but not limited to: congenital long QT syndrome, nephrotic syndrome, glomerulopathy, uncontrolled high blood pressure despite adequate treatment, interstitial lung disease, pulmonary arterial hypertension).
*Effective and appropriate contraception for patients (male and female) of reproductive potential during their entire participation in the study and during 6 months after the end of treatment. Effective
contraception are defined in CTFG Guidelines *Recommendations related to contraception and pregnancy testing in clinical trials* (Appendix 7)
*Negative pregnancy test (serum beta-HCG or urinary test) evaluated in the last week in sexually active females of reproductive potential
*Written informed consent given by the patient / legal representative for treatment

Exclusion criteria

Spontaneous massive intratumour bleeding. Patients with post-operative bleeding will be allowed to enter the study provided the haemorrhage is controlled. Same rule applies for the other post-operative complications (infection, CSF leakage, absence of wound closure, subdural collection*).
*Any other concomitant anti-cancer treatment not foreseen by this protocol
*Any other cancer during the last 5 years
*Uncontrolled intercurrent illness or active infection
*Any other co-morbid condition that in the investigator*s opinion would impair study participation
*Unable for medical follow-up (geographic, social or mental reasons)
*Patient not fulfilling one of the previous eligibility criteria.
*Patient previously treated with irradiation on the brainstem for another neoplasm
*Patient with congenital galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
*Patient not covered by a social security agreement accepted in the treating country if national requirement
*Pregnant or breast feeding women
*PTEN-positivity of the tumor cells (evaluated by IHC)

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-02-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Votubia
Generic name:	everolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-09-2019
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	EUCTR2014-001929-32-NL
ClinicalTrials.gov	NCT02233049
CCMO	NL59879.078.17

Study results

Date completed: 17-09-2024

Summary results
Trial ended prematurely