A phase 2, single arm, European multi-center trial evaluating the efficacy of afatinib as first-line or later-line treatment in advanced chordoma.

Published: 16-05-2017
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Primary objectives- To evaluate the treatment efficacy by progression free survival (PFS) according to RECIST 1.1. - Quality of life assessmentSecondary objectives- To evaluate the treatment efficacy by growth modulation index- To evaluate the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Skeletal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54671

Source
ToetsingOnline

Brief title
CHORD

Condition

- Skeletal neoplasms malignant and unspecified

Synonym
no synonym

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,Boehringer Ingelheim,Boehringer Ingelheim;Chordoma Foundation (patientenvereniging)

Intervention

Keyword: afatinib, chordoma, egfr

Outcome measures

Primary outcome

- PFS >= 12 months in first line treatment and >= 9 months in further line

treatment

- Change from baseline in EORTC QLQ-C30 questionnaire / Brief pain inventory

score

Secondary outcome

Secondary endpoints

- Time to progression during afatinib treatment (TTP2) divided by time to

progression before start of this treatment TTP1 (= growth modulation index)

- Toxicity determined by CTCAE v 4.03 criteria

- Overall survival from start of afatinib treatment

Translational research endpoints

- EGFR pathway and dimerization analysis in archival tumor tissue

- Genome sequence analysis of available tumor samples

- Analysis of circulating biomarkers in patients pre and post treatment

Pharmacokinetic endpoints

- Observed afatinib plasma levels, administered afatinib doses and time between

afatinib doses and sampling. Used to construct:

o a population PK / PD / PG model

o a limited sampling model for afatinib exposure

o a time to event model

o tumor imaging data in relationship to afatinib exposure and genetic data of

the tumor.

Study description

Background summary

Chordomas are rare bone tumors which are accompanied by great morbidity and mortality in case of locoregional recurrence and metastases. There is an unmet need for new systemic treatments for this group of patients. EGFR expression is present on the majority of chordomas and some activity was shown in a previous phase 2 study with EGFR inhibitor lapatinib. Therefore this phase 2 study on the activity of afatinib in chordoma patients in indicated.

Study objective

Primary objectives
- To evaluate the treatment efficacy by progression free survival (PFS) according to RECIST 1.1.
- Quality of life assessment

Secondary objectives
- To evaluate the treatment efficacy by growth modulation index
- To evaluate the safety and tolerability of afatinib in chordoma
- To determine the overall survival after start of treatment

Translational research objectives
- To evaluate whether EGFR pathway and genetic alterations of pre-treatment tumor material correlates with outcome in patients treated with afatinib
- To evaluate circulating predictive and prognostic biomarkers in patients treated with afatinib

Pharmacokinetic research objectives
- To explore the population pharmacokinetics, pharmacogenetics and dynamics of afatinib in metastatic or unresectable chordoma.

o To develop a population pharmacokinetics (PK) / pharmacodynamics (PD) / pharmacogenetic (PG) model using non-linear mixed effects modeling (NONMEM)
o To develop a limited sampling model able to accurately predict afatinib exposure with a limited amount of blood samples
o To develop a time to event model based on the collected data to be able to simulate optimal dosing strategies for afatinib in metastatic or unresectable chordoma patients
o To model tumor imaging data (growth or shrinkage) in relationship to afatinib exposure and genetic data of the tumor

Study design

Phase 2 study with single treatment arm, where patients with advanced chordoma are treated with afatinib. Two different cohorts will be included: 20 patients in whom afatinib will be first-line treatment and 20 patients in whom afatinib will be second or later-line treatment. Afatinib is given in 4-week cycles until disease progression or discontinuation for other reasons. Median progression free survival and quality of life will be primarlity evaluated.

Intervention

Afatinib tablets 40mg once daily continuous in 4-week cycles until disease progression

Study burden and risks

Subjects will visit the study clinic every 4 weeks for an appointment with their doctor, dispensation of study medication, blood checks chemistry/haematology, physical exam and check of vital signs. Visits will take approximately 30-45 minutes, with the exeption of two long days on which PK samples will be taken. Those days patients will be in the clinic for a maximum of 4-8 hours. Further burden:
- Questionnaires on quality of life and pain (2 questionnaires per visit, once every 8 weeks, 5 minutes per questionnaire)
- Keeping up a study medication diary daily (time of dosing, dose of afatinib)

Blood withdrawals:
- Every 4 weeks haematology / chemistry 10 mL total
- Translational research: Baseline, at C4D1, C7D1 and at end of treatment (< 30 days of last dose afatinib), 40mL drawn for translational research
- Draws for pharmacokinetic research; 4 days / 12 draws via canulla in total: cycle 1 day 1 (C1D1) 20mL, C1D15 30 mL, C3D1 5mL, C5D1 5 mL.

Possible risks:
- Biopsy: ultrasound / CT guided tumor biopsy, risk of bleeding / infection (these will be performed in the minority of subjects, since most patients will

have archival tumor tissue available and do not need a fresh biopsy)
- Venapuncture / cannula: low risk of bleeding / infection / pain
- Study medication: side-effects (skin rash 70%, diarrhea 95%, mucositis 70%, nail infections 50% etc, see patient information)

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

- Locally advanced or metastatic, pathologically proven, EGFR expressing chordoma, not amenable for local therapies , - Patients of 18 years and up , - Documented radiographic progression of disease according to RECIST 1.1 criteria in last 6 months, with interval between 2 pre-treatment scans of <= 6 months - ECOG Performance status <= 2 , - Adequate bone marrow function (Hb >= 6.0 mmol/L, absolute neutrophil count >= 1.5 x 109/L, platelets >= 75 x 109/L), - An

adequate renal function with GFR >= 45 ml/min calculated by Cockroft-Gault formula, - Total Bilirubin <= 1.5 times upper limit of normal (ULN) (Patients with Gilbert*s syndrome total bilirubin must be <=4 times institutional upper limit of normal)., - Aspartate amino transferase (AST) or alanine amino transferase (ALT) <= 3 times ULN (if related to liver metastases <= 5 times ULN), - Ability to swallow medication, - Recovered from any previous therapy related toxicity to <= grade 1 at study entry (except for stable sensory neuropathy <= grade 2 and alopecia), - Availability of archival tumor material for review (if not please obtain a new tumor biopsy), - Written signed informed consent, - Ability to adhere to the study visits and all protocol requirements

Exclusion criteria

- Life expectancy of less than 3 months, - No measurable lesions according to RECIST 1.1, - Known hypersensitivity to afatinib, - Major surgery less than 4 weeks prior to start of treatment , - Previous treatment with any other investigational agents within 14 days of first day of study drug dosing , - History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of >= 3, unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to inclusion., - Known pre-existing interstitial lung disease, - Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g. Crohn*s disease, ulcerative colitis, chronic diarrhea, malabsorption) , - Known active hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier., - Systemic anti-cancer therapy within 28 days prior to the first dose of study drug , or radiotherapy to an index (or target)lesion within 21 days prior to the first dose of study drug , - Requiring treatment with any of the prohibited concomitant medications listed in Section 6.3.9 that cannot be stopped for the duration of trial participation, - Pregnant or lactating women, - Other invasive malignancies diagnosed within the last 5 years, except non-melanoma skin cancer and localized cured prostate and cervical cancer, - Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient*s ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-06-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	giotrif
Generic name:	afatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-05-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	29-05-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO
Date: 25-03-2019

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 23-01-2020

Application type: Amendment

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Approved WMO
Date: 29-01-2020

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 06-05-2020

Application type: Amendment

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Approved WMO
Date: 22-09-2020

Application type: Amendment

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Approved WMO
Date: 01-12-2020

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 02-02-2021

Application type: Amendment

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Approved WMO
Date: 08-02-2021

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 06-08-2022

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 22-08-2022

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 07-01-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 16-01-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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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	EUCTR2016-002766-31-NL
ClinicalTrials.gov	NCT03083678
CCMO	NL59676.058.17