A clinical phase I, open-label PET study with 89Zr CriPec docetaxel in patients with solid tumours to assess biodistribution and tumour accumulation of 89 Zr CriPec docetaxel

Published: 06-12-2017
Last updated: 12-04-2024

The primary objectives of this study is to determine whether uptake of 89Zr CriPec® docetaxel in tumour lesions can be detected and quantified

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON50409

Source
ToetsingOnline

Brief title
PICCOLO

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
cancer oncology

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Cristal Therapeutics

Intervention

Keyword: CriPec docetaxel, nanoparticle, PET scan, Zirconium

Outcome measures

Primary outcome

The primary endpoint of this study is detection (visual and quantitative) of 89Zr CriPec® docetaxel in tumour lesions (the long axis diameter of a visually assessable and quantifiable lesion must be * 2 cm) .

The five largest lesions will be used for evaluation:

- Visually: present/absent; present being as focally enhanced uptake on the PET scan with optimal contrast (2-96 h post injection).
- Quantitatively: same tumour lesions measured in Standardized Uptake Value (SUV) using tumour volumes of interest (VOI). % Injected dose (ID)/ml above background and above blood will be determined.

To prevent undetectable uptake due to size the short axis diameter of at least one measurable lesions must be * 2 cm for each patient. Liver lesions may be excluded for analysis if excessive sequestering of 89Zr CriPec® docetaxel in healthy liver is observed.

Secondary outcome

The secondary endpoints of the study are:

* Dosimetry of 89Zr CriPec® docetaxel:

o Organ dose (mSv) - recorded for each organ

o Effective dose (mSv) * a single value for each subject

* Define the optimal time point for PET imaging after 89Zr CriPec® docetaxel administration

* Pharmacokinetics of 89Zr CriPec® docetaxel and total docetaxel

* Biodistribution of low dose dose89Zr CriPec® docetaxel before and after administration of therapeutic dose of CriPec® docetaxel (quantified with %ID 89Zr CriPec® docetaxel)

* Adverse Effects using Common Terminology Criteria Adverse Events, version 4.0 (CTCAE 4.0)

* Correlation between side effects of CriPec® docetaxel and uptake of 89Zr CriPec® docetaxel in normal tissue

* The correlation between tumour (quantification measures of) targeting of 89Zr CriPec® docetaxel and response to therapy.

Study description

Background summary

Nanoparticle compounds, such as CriPec® docetaxel are designed to have an improved efficacy while maintaining acceptable safety and tolerability profiles compared to the standard docetaxel. The hypothesis is that these compounds stay longer in circulation than the native drug, and therefore docetaxel accumulates in tumour lesions due to the retention of docetaxel in the nanoparticle (the enhanced penetration and retention effect (EPR)). Subsequent release of docetaxel from the entrapped particles will allow a local anti-tumour effect, whilst docetaxel exposure in non-tumour tissue will remain limited. It is expected that CriPec® docetaxel has a better systemic distribution as compared to docetaxel including a higher accumulation in the tumour. Indeed, as

described in preclinical experiments in rats, the Cmax and AUC following the administration of CriPec docetaxel was approximately 150-200 times greater than the Cmax and AUC of total docetaxel following the administration of docetaxel at the same dose.
In order to prove that this mechanism of action indeed leads to selective accumulation in tumour lesions in the patient, this study will investigate in vivo imaging of the entire patient using 89Zr labelled CriPec® docetaxel.
PET imaging with 89Zr labelled tracers in patients have been described for many different monoclonal antibodies (Jauw 2016). PET imaging is a feasible way of obtaining quantitative information on the levels of drug present in normal as well as tumour tissues throughout the body simultaneously and at multiple time points without being as invasive as multiple biopsies. Nanoparticles have similar half-life as mAb, the long lived tracer 89Zr (t* = 78 h) is ideally suited to label CriPec® docetaxel. In a non-clinical qualification study, CriPec® docetaxel was conjugated to the chelator Desferal and subsequently radiolabelled with 89Zr using procedures described previously [Perk 2006]. Please see the IMPD for further details.

The purpose of this proof-of-concept study is to determine uptake of 89Zr CriPec® docetaxel in tumour lesions of patients with solid tumours with histological types for which treatment with a taxane is an appropriate option. The initial aim will be to establish if low dose 89Zr CriPec® docetaxel accumulation in tumour lesions can be determined in the first 3 patients. In these same patients linearity of 89Zr CriPec® docetaxel PK at low dose and during treatment with CriPec® docetaxel at the RP2D of 60 mg/m2 will be determined. In addition, unlabelled CriPec® docetaxel will be administered at variable doses (2-5 patients per cohort) before low dose of 89Zr CriPec® docetaxel to investigate the existence of a sink and gain further information on in vivo PK of 89Zr CriPec® docetaxel. Dose levels will be chosen based on the results obtained so far. In case of negative results (no visual tumour uptake of 89Zr CriPec® docetaxel in tumour lesions >2 cm outside the liver) in the first 3 patients, the study will be discontinued.

Study objective

The primary objectives of this study is to determine whether uptake of 89Zr CriPec® docetaxel in tumour lesions can be detected and quantified

Study design

A clinical phase I, open-label, immune-PET study with [89Zr] CriPec® docetaxel in patients with solid tumours to assess biodistribution and tumour accumulation of [89Zr] CriPec® docetaxel

After inclusion an [18F]-FDG PET scan will be performed to delineate viable tumour lesions. On day 1, patients will receive a low dose of [89Zr] CriPec®

docetaxel (corresponding to approximately 0.1-2 mg docetaxel) followed by maximally 3 [89Zr]-PET scans (timing of PET scan can be adapted depending on results obtained, within timeframe of 2 h * 9 days after administration) to evaluate biodistribution and tumour uptake. Two weeks later, the patients will receive unlabelled CriPec® docetaxel up to the RP2D that was determined to be safe in the phase I NAPOLY trial (CT-CL01), immediately followed by a second low dose of [89Zr] CriPec® docetaxel and maximally 3 [89Zr]-PET scans (timing of PET scan can be adapted depending on results obtained, within timeframe of 2 hrs * 9 days after administration) to evaluate biodistribution and tumour uptake with therapeutic dosage.

Patients will continue to receive unlabelled CriPec® docetaxel every 3 weeks at the RP2D determined in the NAPOLY trial until disease progression, unacceptable toxicity, or discontinuation for any other reason.

Intervention

All patients will undergo a fluorodeoxyglucose (FDG)-PET scan within 14 days before Run-in Day 1 to identify metastatic lesions and to precisely demarcate viable tumour tissue.
The first 3 patients will undergo 3 whole-body PET scans at 2 (for dosimetry purposes), 48 and 96 h after the first dose of 89Zr CriPec® docetaxel (where t=0 is the time of administration of 89Zr CriPec® docetaxel) and 2 whole body PET scans at 48 and 96 h after the second dose of 89Zr CriPec® docetaxel.
The next patients will undergo 2-3 PET scans after each administration of 89Zr CriPec® docetaxel, with a maximum of 5 89Zr PET scans/patient, < 9 days after each administration. The timing of these PET scan will be determined based on the data gathered in the first 3 patients.

PK assessments:
Whole blood and plasma concentrations of 89Zr CriPec® docetaxel and plasma concentrations of total docetaxel will be measured and PK parameters in whole blood and plasma (Cmax, AUC, CL, Vss and t1/2), respectively will be calculated in the first 3 patients.

Study burden and risks

For the patient the total dose administration of 2 times 37 MBq of 89Zr CriPec® docetaxel is expected to be around 40 mSv. Low dose CT scans used for attenuation correction will give an additional dose of 3 mSv for low dose CT.
The radiation dose from an FDG-PET scan is usually around 4 mSv, with 3 mSv for low dose CT. The total effective dose is expected to be around 62 mSv for the first three patients. As a comparison, natural cosmic radiation exposure in the Netherlands during is 2,5 mSv per year.

The side effects of CriPec docetaxel are the same as for the known chemotherapy

docetaxel:
Increased risk of gettinf an infection, breathlessness, tiredness and weakness (fatigue) during and after treatment, hair loss, skin rash, fluid build up, discoloured fingernails.
Soreness, redness and peeling of skin on hand and feet, sore mouth, diarrhoea, peripheral sensitive neuropathy, allergic reactions, watery eyes.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age older or equal to 18 years
2. A pathologically confirmed diagnosis of advanced, recurrent and progressive cancer that is refractory to standard therapy or for which no standard therapy exists and where treatment with a taxane is an appropriate treatment option

3. Measurable or evaluable disease according to RECIST criteria v.1.1. Patient must have at least one measurable lesion with a long axis diameter of > 2 cm.
4. Performance status (WHO scale/ECOG) smaller or equal than 2
5. Estimated life expectancy of at least 12 weeks
6. Toxicities incurred as a result of previous anti-cancer therapy (radiation therapy, chemotherapy, or surgery) must be resolved to * grade 2 (as defined by CTCAE version 4.0)
7. ANC equal or> 1.5 x 109/L; platelets equal or > 100 x 109/L; Haemoglobin equal or >* 6.0 mmol/L (equal or >* 9.6 g/dL)
8. Creatinine ** 1.5 x upper limit of normal (ULN); or creatinine clearance equal or > 60 mL/min (Cockcroft-Gault)
9. Serum bilirubin ** 1.5 x ULN; alkaline phosphatase, ASAT and ALAT ** 2.5 x ULN, unless related to liver metastases, in which case ** 5 x ULN is allowed
10. Written informed consent according to local guidelines

Exclusion criteria

* Less than 4 weeks since the last treatment with other anti-cancer therapies, (i.e. endocrine therapy, immunotherapy, radiotherapy, chemotherapy, etc.), less than 8 weeks for cranial radiotherapy, and less than 6 weeks for nitrosoureas and mitomycin C prior to first study treatment
* A history of grade 2 or higher skin toxicity as a result of prior treatment with taxanes
* If excessive sequestering of 89Zr CriPec ® docetaxel in healthy liver is observed in the first 3 patients, patients with only liver lesion will not be eligible
* Current or recent (within 28 days of first study treatment) treatment with another investigational drug or participation in another investigational study
* Current malignancies at other sites, with exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin
* Major surgical procedure (including open biopsy, excluding central line IV and port-a-cath) within 28 days prior to the first study treatment, or anticipation of the need for major surgery during the course of the study treatment
* Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100mm Hg)
* Grade *2 motor or sensory neuropathy symptoms (as defined by CTCAE version 4.03)
* Known hypersensitivity to any of the study drugs or excipients or taxanes
* Any active skin condition associated with impaired skin integrity exposing the patient at risk to develop skin toxicity
* Clinically significant (i.e. active) cardiovascular disease defined as:
* Stroke within * 6 months prior to first study treatment;
* Transient Ischemic Attack (TIA) within * 6 months prior to first study treatment;

* Myocardial infarction within * 6 months prior to first study treatment;
* Unstable angina;
* New York Heart Association (NYHA) Grade II or greater Congestive Heart Failure (CHF);
* Serious cardiac arrhythmia requiring medication;
* Clinically relevant pathologic findings in electrocardiogram (ECG);
* Left Ventricle Ejection Fraction (LVEF) by MUGA or ECHO < 50%
13. Patients who are pregnant or breastfeeding
14. Absence of effective means of contraception as of Run-in Day 1 in female patients of childbearing potential (defined as <2 years after last menstruation and not surgically sterile) or in male patients who are not surgically sterile and who have female partners of childbearing potential
15. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, drug or alcohol abuse, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment-related complications

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):	09-04-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[89Zr]-Df-CriPec docetaxel
Generic name:	nvt

Product type:	Medicine
Brand name:	CriPec docetaxel
Generic name:	nvt

Ethics review

Approved WMO Date:	06-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-0034664-1-NL
ClinicalTrials.gov	NCT03712423
CCMO	NL63373.029.17