A Phase I Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of CriPec® docetaxel in Patients with Solid Tumours.

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Circulating CriPec docetaxel nanoparticles are designed to be in a higher degree than the original compound (docetaxel) to be trapped in tumor tissue due to the enhanced penetration and retention (EPR) effect. Subsequent release of docetaxel from...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44828

Source
ToetsingOnline

Brief title
NAPOLY (Nanoparticle Polymeric Docetaxel)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
solid tumours / abnormal cell division in a particular organ

Research involving
Human

Sponsors and support

Primary sponsor: Cristal Therapeutics
Source(s) of monetary or material Support: Cristal Therapeutics

Intervention

Keyword: docetaxel, nanomedicines, solid tumours

Outcome measures

Primary outcome

The primary endpoints for Part 1 are:

• The incidence of Grade 3 or 4 adverse events (AEs) defined as dose-limiting toxicities Dose Limiting Toxicities (DLTs).

• PK parameters including:

o Plasma levels of total and released docetaxel up to 1 week after 1st dose: Cmax, Tmax, AUClast, AUCinf, Thalf, lambda z, Cl and Vss in relation to body surface area (m2) where applicable. Cmax, Tmax, AUClast, AUCinf, Thalf, lambda z, Cl, and Vss will also be determined after the 2nd dose.

o Comparison of the PK profile of total and released docetaxel in repeated dosing versus initial dosing.

The primary endpoints for Part 2 are:

• Safety and tolerability profile of CriPec docetaxel given every two weeks (Q2W) including the incidence of Dose Limiting Toxicities (DLTs)

• PK parameters in Q2W dosing: plasma levels of total and released docetaxel after single and repeated dosing.

The primary endpoints of Part 3 are:

• Safety and tolerability profile of CriPec docetaxel given Q3W including the

incidence of DLTs

• Plasma levels of total and released docetaxel after single and repeated

dosing of CriPec docetaxel given Q3W

Secondary outcome

The secondary endpoint for Part 1 is the response rate and duration of response

per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

The secondary endpoint for Part 2 is the response rate and duration of response

per RECIST Version 1.1.

The secondary endpoints for Part 3 are:

• Response rate and duration of response per RECIST Version 1.1.

• Level of total docetaxel in tumour tissue biopsies

Study description

Background summary

Cristal Therapeutics has developed a proprietary technology (CriPec) to transform drug molecules into nanoparticulate compounds, thereby creating nanomedicines that are believed to improve efficacy while maintaining acceptable safety and tolerability profiles. With this technology, a nanoparticle product containing docetaxel (CriPec docetaxel) has been designed. CriPec docetaxel consists of docetaxel conjugated to a linker agent, and this docetaxel-linker conjugate is covalently entrapped in a stabilised, CriPec nanoparticle.
Docetaxel (Taxotere®) is a member of the taxane family. Docetaxel has significant activity against several tumour types and is approved for the

treatment of locally advanced or metastatic breast, non-small cell lung cancer, head and neck cancer, gastric cancer and hormone refractory metastatic prostate cancer [Taxotere® label text 2014]. Docetaxel is active as single agent and it has also demonstrated synergistic effects with other cytotoxic agents, angiogenesis inhibitors, trastuzumab and radiation therapy. Docetaxel is typically applied in 3-weekly i.v. schedules at doses ranging from 60 to 100 mg/m2, administered as a 1-hour infusion. The primary dose-limiting toxicity in early studies of docetaxel was neutropenia, and even at the therapeutic doses given in current practice, neutropenia persists as a frequent toxicity effect. In addition, weekly i.v. schedules, instead of 3-weekly i.v. schedules, have been used, as these schedules cause less hematologic toxicity and equal or even better efficacy [Schuette 2005, Wailoo 2009]. Docetaxel treatment may cause epiphora or excessive tearing. This toxicity can occasionally be dose-limiting [Kintzel 2006]. Other toxicities seen with docetaxel include peripheral edema, interstitial pneumonitis, asthenia, fatigue, nausea and vomiting. Furthermore, the administration of Docetaxel is associated with severe hypersensitivity reactions due to the excipient polysorbate 80 (Tween 80) in the pharmaceutical formulation of Taxotere® [Engels 2007]. Docetaxel is metabolized extensively by the cytochrome P450 CYP system, with the 3A family representing the major route of inactivation.

Study objective

Circulating CriPec docetaxel nanoparticles are designed to be in a higher degree than the original compound (docetaxel) to be trapped in tumor tissue due to the enhanced penetration and retention (EPR) effect. Subsequent release of docetaxel from the embedded particles are a local anti-tumor effect, while exposure of non-tumor tissue to docetaxel remains limited. It is expected that CriPec docetaxel shows a better systemic distribution and a higher accumulation in the tumor as compared to docetaxel.

The primary objectives for Part 1 are:
• To evaluate the toxicity profile of escalating doses CriPec docetaxel and to determine the MTD and the RP2D of CriPec docetaxel given every 3 weeks (Q3W)
• To characterize the PK profile of CriPec docetaxel

The secondary objective for Part 1 is:
• to assess early signs of anti-tumour activity of CriPec docetaxe l.

The primary objective for Part 2 are:
• To identify the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dosage of CriPec docetaxel given every 2 weeks (Q2w)..
• To ensure absence of cumulative systemic accumulation of CriPec docetaxel upon repeated administration

The secondary objective of Part 2 is:
• To asses early signs of anti-tumour activity (response rate + duration

of response) of CriPec docetaxel in patients with tumour types of which treatment with taxane is an appropriate treatment option.

The primary objective for part 3 are:
• To confirm the RP2D of CriPec docetaxel given every 3 weeks (Q3W) with premedication
• To ensure absence of cumulative systemic accumulation of CriPec docetaxel upon repeated administration

The secundary objective for part 3 are:
• To assess early signs of anti-tumour activity (response rate + duration of response) of CriPec docetaxel in patients with tumour types for which treatment with a taxane is an appropriate treatment option.
• To evaluate the level of total docetaxel in tumour tissue biopsies

Study design

This is a three-part, open-label, safety, PK, and preliminary efficacy study of CriPec docetaxel administered i.v. every 21 days (Q3W) in Part 1 in previously treated patients with progressive, solid tumours and who have failed treatment with standard systemic treatmentIn In Part 2 the dosage (dose level and frequency) at which CriPec docetaxel can be given without cumulative toxicities will be further optimized to reach a RP2D. Patients In Part 2, two dose escalations will be done. First, approximately 12 patients in Part 2A will be treated at escalating doses of CriPec docetaxel given Q2W. The dose escalation process for CriPec docetaxel given Q2W will follow the same rules as in Part 1, but has a DLT window of 8 weeks (2 cycles). To further prevent or mitigate skin toxicity, in Part 2B a second dose escalation will be started at the MTD defined in Part 2A, but these patients will receive premedication with oral dexamethasone.
In Part 3 the RP2D of CriPec docetaxel Q3W determined in Part 1 will be explored with premedication

Intervention

Upon completion of Cycle 1 and in the absence of progressive disease (PD) or unacceptable toxicity, patients in all parts of the study may receive additional cycles of treatment, with ongoing safety monitoring, beginning on Day 1 of Cycle 2. CriPec docetaxel will be administered Q3W during this period (21-day cycles). It should be the intention to treat a patient in all cycles at the dose level assigned at Cycle 1.
For female patients at the beginning of every new cycle and at EOT a pregnancytest will be performed.
Patients may continue to receive additional cycles of treatment until the patient experiences disease progression, unacceptable toxicity, request by patient or physician to discontinue treatment, death, or termination of the

study by the sponsor. The duration of patient participation may therefore vary. Study visits should be scheduled relative to day 1 of each cycle.

All patients in Part 1 and 3 should return to the clinic for End of Treatment (EOT) assessments 22 (±3) days after the last dose of CriPec docetaxel has been administered.

If a patient has discontinued treatment due to abnormal blood values, these will be followed up weekly until they have normalised.
Twenty-eight (±3) days after EOT a vital status visit will be conducted (for Part I and Part 2). This visit may be conducted by telephone.

Study burden and risks

Docetaxel (Taxotere®) is an established anti-cancer drug and its toxicological profile is well known. Docetaxel is the active ingredient of the CriPec docetaxel nanoparticle formulation. The safety and efficacy of CriPec docetaxel has not yet been studied in humans. However, preclinical studies have been performed to determine the efficacy and safety of CriPec docetaxel prior to the start of the phase I study. In toxicology studies it was demonstrated that CriPec docetaxel has a similar toxicity profile as the active component with the addition of vacuolation of reticuloendothelial macrophages by the nanoparticle formulation. This is considered an adaptive change, but not a toxic response. The minimum toxic dose in rats treated intermittently was higher for CriPec docetaxel compared to Taxotere®. In preclinical efficacy experiments CriPec docetaxel showed significant better tumour growth inhibition and survival benefit in rodent xenografts with breast and gastric cancer compared to regular docetaxel.
Safe and effective drug delivery of docetaxel to tumours remains challenging. CriPec docetaxel is potentially capable of delivering more docetaxel within a favourable therapeutic window. Based on the medical need, and the positive outcome of the preclinical safety and efficacy studies of CriPec docetaxel, clinical studies are necessary to evaluate CriPec docetaxel*s clinical potential in the treatment of malignancies for which treatment with a taxane is an appropriate treatment option.

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. Age >= 18 years at signing of Informed Consent Form (ICF).
2. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
3. Estimated life expectancy of at least 12 weeks.
4. Ability and willingness to give written informed consent and to comply with the requirements of the study.
In addition to the above listed eligibility criteria, the following criteria are applicable:
Part 1
5. Patients with pathologically confirmed diagnosis of advanced, recurrent and progressive solid tumours that are refractory to standard therapy or for whom no standard therapy exists and with measurable or evaluable disease according to RECIST 1.1.
Part 2 and part 3
6. Patients with pathologically confirmed diagnosis of advanced, recurrent and progressive cancer with measurable disease according to RECIST 1.1 that are refractory to standard therapy or for whom no standard therapy exists and where treatment with a taxane is an appropriate treatment option

Exclusion criteria

A patient who meets ANY of the following criteria at screening and/or <=3 days of Cycle 1 Day 1 prior to Investigational Product administration (unless otherwise noted below) is not

eligible for this study:
1. Less than 4 weeks since the last treatment of chemotherapy, biological therapy, immunotherapy or systemic radiotherapy (except palliative radiation delivered to <20% of bone marrow), and less than 6 weeks for nitrosoureas and mitomycin C prior to Cycle 1 Day 1.
2. Current or recent (within 4 weeks prior to Cycle 1 Day 1) treatment with another Investigational Product or participation in another investigational interventional study.
3. Symptomatic brain metastases.
4. Toxicities incurred as a result of previous anti-cancer therapy (radiation therapy, chemotherapy, or surgery) that have not resolved to <= grade 2 (as defined by CTCAE version 4.03).
5. Abnormal lab results which could indicate inadequate bone marrow function, as evidenced by any of the following at screening and/or <= 3 days of Cycle 1 Day 1 prior to Investigational Product :
* Absolute Neutrophil Count (ANC) < 1.5 x 109/L.
* Platelet count < 100 x 109/L.
* Haemoglobin < 6.0 mmol/L (< 9.6 g/dL).
The patient may not have received a transfusion or growth factors for these abnormalities in the 7 days prior to Cycle 1 Day 1.
Inadequate liver function as evidenced by any of the following at screening and/or <= 3 days of Cycle 1 Day 1 prior to Investigational Product Administration:
6. Serum (total) bilirubin > 1.5 x the Upper Limit of Normal (ULN) for the institution if no liver metastases (> 2 x ULN in patients with liver metastases).
7. AST or ALT > 2.5 x ULN if no liver metastases (> 5x ULN in patients with liver metastases).
8. Alkaline phosphatase levels > 2.5 x ULN if no liver metastases (> 5 x ULN in patients with liver metastases, or > 10 x ULN in patients with bone metastases).
9. International Normalized Ratio (INR) >1.3, consequence of reduced hepatic production of Vitamin K.
10. Hepatitis B surface antigen or hepatitis C positivity in combination with abnormal liver function tests as determined by the Investigator.
11. Medical history of:
* Non-alcoholic steatohepatitis (NASH).
* History of human immunodeficiency virus (HIV) antibody positive or use of antiretroviral therapy.
* Alcoholic and autoimmune hepatitis.
* Ischemic hepatitis, inadequate liver function due to cardiovascular dysfunction or impaired liver oxygenation (e.g. due to hypotension or right heart failure).
Inadequate renal function as evidenced by any of the following at screening and/or <= 3 days of Cycle 1 Day 1 prior to Investigational Product Administration:
12. Serum creatinine > 1.5 x ULN.
13. Estimated Glomerular Filtration Rate of < 50 mL/min/1.73m2 calculated by Modification of Diet in Renal Disease (MDRD) formula or creatinine clearance of < 50 mL/min calculated by Cockcroft-Gault.
Clinically significant (i.e. active) cardiovascular disease as evidenced by any of the following at screening and/or Cycle 1 Day 1 (unless otherwise noted below):
14. Stroke within 6 months prior to Cycle 1 Day 1.
15. Transient Ischemic Attack (TIA) within 6 months prior to Cycle 1 Day 1.

16. Myocardial infarction within 6 months prior to Cycle 1 Day 1.
17. Unstable angina.
18. New York Heart Association (NYHA) Grade II or greater Congestive Heart Failure at screening.
19. Serious cardiac arrhythmia requiring medication.
Other at screening and/or Cycle 1 Day 1 (unless otherwise noted below)::
20. Patients who are pregnant or breastfeeding.
21. Absence of effective means of contraception as of Cycle 1 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.
22. Major surgical procedure (including open biopsy and excluding central line intravenous catheter) within 28 days prior to Cycle 1 Day 1, or anticipation of the need for major surgery during the course of the study treatment.
23. Grade >=2 motor or sensory neuropathy symptoms (as defined by CTCAE version 4.03).
24. Known hypersensitivity to any of the Investigational Product*s excipients or taxanes.
25. History of drug or alcohol abuse in the opinion of the Investigator within 3 years before screening.
26. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk for treatment-related complications.
27. Any active skin condition associated with impaired skin integrity exposing the patient at risk to develop skin toxicity
28. Current treatment with strong inhibitors and inducers of Cytochrome P450 family 3A (CYP3A)
Part 2B and Part 3:
29. Known hypersensitivity to dexamethasone or any other reason that would make the patient not eligible to receive dexamethasone

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-10-2015
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CriPec Docetaxel
Generic name:	----------

Ethics review

Approved WMO Date:	28-04-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	29-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2018
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	EUCTR2014-004518-27-NL
ClinicalTrials.gov	NCT02442531
CCMO	NL52166.078.15