A multi-institutional open label, trial evaluating the efficacy of Gemcitabine and Docetaxel in patients with relapsed or refractory metastatic colorectal adenocarcinoma with methylated CHFR and/or microsatellite instability (MSI) phenotype.

Published: 20-02-2014
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Determine the efficacy of combination gemcitabine and docetaxel chemotherapy in the treatment of metastatic colorectal cancer with CHFR and/or MSI phenotype

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON44946

Source
ToetsingOnline

Brief title
GemDoc

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,VU medisch centrum divisie I beheer bv.

Intervention

Keyword: CHFR, Docetaxel, Gemcitabine, metastatic colorectal carcinoma

Outcome measures

Primary outcome

Primary Objectives

Determine the response rate of gemcitabine and docetaxel combination therapy

for treatment of relapsed or refractory metastatic colorectal adenocarcinoma

with methylation of CHFR and/or microsatellite instability

Secondary outcome

Secondary Objectives

Determine the progression free survival with gemcitabine and docetaxel

combination therapy in the selected patient population

Determine the overall survival with gemcitabine and docetaxel combination

therapy in the selected patient population

Assess CHFR methylation in circulating tumor DNA and compare to CHFR

methylation observed in tumor tissue

Assess changes in CHFR methylation in circulating tumor DNA over the time of

therapy to determine if CHFR demethylation occurs as a predictor of progression

Analyze tumor tissue using a global methylation approach to develop a more

robust predictive signature of treatment response

Evaluate changes in quality of life for patients treated with this regimen by

serial measurements using the QLQ-C30 and QLQ-CR29 questionnaire.

Study description

Background summary

*CHFR is a checkpoint protein which causes cell cycle arrest and associated chemotherapy resistance when exposed to microtubule inhibitors
*Epigenetic silencing of CHFR expression via CpG promoter methylation has been shown to increase sensitivity to microtubule inhibitors
*Microsatellite instability (MSI-H) colorectal cancer is associated with sensitivity to gemcitabine
*Methylation of CHFR and/or microsatellite instability is/are present in approximately 25-40% of all colorectal adenocarcinoma tumors, with significant overlap of CHFR methylation with MSI-H
*Gemcitabine and docetaxel have been safely combined in the treatment of non-small cell lung cancer and breast cancer
*Gemcitabine and docetaxel combination therapy has demonstrated significant preclinical activity in colorectal cancer cell lines with CHFR and/or MSI phenotype

Study objective

Determine the efficacy of combination gemcitabine and docetaxel chemotherapy in the treatment of metastatic colorectal cancer with CHFR and/or MSI phenotype

Study design

Patients metastatic colorectal carcinoma who are either intolerant or refractory to one or more standard lines of chemotherapy will be asked to participate. After informed consent archival tumor tissue will be tested for MSI and CHFR promoter methylation. If tested positive for one of these tumor characteristics, and all othere eligibility criteria are met, study treatment will be commenced.

Patients will receive intravenous gemcitabine 500mg/m2 on days 1 and 8 and

docetaxel 70mg/m2 on day 8 of each 21 day cycle
Patients will receive filgrastim (G-CSF) on days 9 through 15 or pegfilgrastim 6mg on day 9 or 10 of each cycle
Patients will be evaluated for toxicity prior to receiving each cycle and every 6 weeks for response using RECIST criteria 1.0
A minimum of 10 and a maximum of 40 patients will be enrolled

Intervention

Patients will receive intravenous gemcitabine 500mg/m2 on days 1 and 8 and docetaxel 70mg/m2 on day 8 of each 21 day cycle
Patients will receive filgrastim (G-CSF) on days 9 through 15 or pegfilgrastim 6mg on day 9 or 10 of each cycle

Study burden and risks

The study treatment is an approved chemotherapeutic regime for other types of cancer and deemed safe.
Side effects of systemic therapy can occur and patients can experience side effects or complications of the blood sampling . The risks of participating in the study are limited, and if successful, study treatment may benefit the subject as well. The information that we learn from this study has the potential to improve therapy for patients with refractory colorectal cancer, and may benefit individuals who are diagnosed with this disease in the future.

Contacts

Public
Vrije Universiteit Medisch Centrum

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

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

histologically or cytologically confirmed metastastic or unresectable colorectal adenocarcioma measurable disease
intolerant or refractory to one or more standard lines of chemotherapy
age>18
ECOG 0-1
life expectancy of greater than 12 weeks
normal organ and marrow function
MSI phenotype of archival tissue biopsy determined by PCR and IHC
CHFR gene promoter methylation in archival tissue biopsy
ability to understand and willingness to sign a written informed consent document

Exclusion criteria

chemotherapy or radiotherapy within 4 weeks prior to entering study, or not being recovered from adverse events.
receiving any other investigational agents
known brain metastases
history of allergic reactions attributed to cmpounds of simiar chemical or biological composition to gemcitabine or docetaxel.
receiving any medications or substances thtat are inhibitors or inducers of CYP3A4
uncontrolled intercurrent illness
pregnant women
HIV positive patients

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):	26-05-2015
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Docetaxel for Injection
Generic name:	Docetaxel
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Gemcitabine for injection
Generic name:	Gemcitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2016
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	EUCTR2013-005086-40-NL
ClinicalTrials.gov	NCT01639131
CCMO	NL47205.029.14