Randomized phase II trial evaluating the efficacy of FOLFOX alone, FOLFOX plus bevacizumab and FOLFOX plus panitumumab as perioperative treatment in patients with resectable liver metastases form wild type KRAS colorectal cancer. EORTC 40091.

Published: 22-01-2013
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Primary objective: to detect an increase in progression free survival (PFS*, see chapter 7.3.6) rate at 1 year in each experimental arm (mFOLFOX6 + bevacizumab or panitumumab) compared to mFOLFOX6 alone arm as perioperative treatment for resectable...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON39488

Source
ToetsingOnline

Brief title
BOS 2

Condition

- Metastases

Synonym
liver cancer, liver metastasis

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC

Intervention

Keyword: bevacizumab, FOLFOX, Panitumumab, resectable liver metastases

Outcome measures

Primary outcome

to detect an increase in progression free survival (PFS*, see chapter 7.3.6)

rate at 1 year in each experimental arm (mFOLFOX6 + bevacizumab or panitumumab)

compared to mFOLFOX6 alone arm as perioperative treatment for resectable liver

metastasis from wild type Kirsten rat sarcoma viral oncogene homolog (KRAS)

colorectal cancer (CRC).

Secondary outcome

to assess the pathological response rate and detect an increase in major

pathological response rate between mFOLFOX6 alone arm and each experimental

arm. Others objectives are correlation between pathological response and

disease free survival (DFS), resection rate, response rate, PFS*, overall

survival and safety.

Study description

Background summary

The current practice for patients with unresectable metastatic CRC is based on
a combination of

chemotherapy and target therapy (Ref. 10). Cetuximab, bevacizumab and panitumumab are the only
licensed targeted drugs, usually used in combination with chemotherapy, presenting relatively high
response rates however little effect on survival.

Retrospective analyses across randomized clinical trials suggest that anti-EGFR monoclonal antibodies,
such as panitumumab, are not effective for the treatment of patients with mCRC containing KRAS
mutations. In these trials, patients received standard of care (i.e., best supportive care or chemotherapy)
and were randomized to receive either an anti-EGFR antibody (cetuximab or panitumumab) or no
additional therapy. In all studies, investigational tests were used to detect KRAS mutations in codon 12 or
13.

Study objective

Primary objective: to detect an increase in progression free survival (PFS*, see chapter 7.3.6) rate at 1 year in each experimental arm (mFOLFOX6 + bevacizumab or panitumumab) compared to mFOLFOX6 alone arm as perioperative treatment for resectable liver metastasis from wild type Kirsten rat sarcoma viral oncogene homolog (KRAS) colorectal cancer (CRC).
Secondary objective: to assess the pathological response rate and detect an increase in major pathological response rate between mFOLFOX6 alone arm and each experimental arm. Others objectives are correlation between pathological response and disease free survival (DFS), resection rate, response rate, PFS*, overall survival and safety.

Study design

This is an open label, randomized, multi-center, 3-arm late phase II study.
Arm A: modified FOLFOX6 before and after surgery
Arm B: modified FOLFOX6 + Bevacizumab before and after surgery
Arm C: modified FOLFOX6 + Panitumumab before and after surgery

Intervention

Arm B = mFOLFOX6 + Bevacizumab (experimental) + surgery
- mFOLFOX6 plus Bevacizumab 5 mg/kg D1 every 2 weeks

Arm C = mFOLFOX6 + Panitumumab (experimental) + surgery
- mFOLFOX6 plus Panitumumab 6 mg/kg D1 every 2 weeks
The perioperative treatment consist of a total of 12 cycles of study treatment

(6 cycles pre- and 6 cycles post-surgery) planned to last for 12 weeks each. Surgery must be performed within 2 to 4 weeks after the end of last cycle of pre-operative chemotherapy. For patients randomized to arm B, bevacizumab will be omitted in the sixth cycle i.e. the cycle preceding surgery.

Arm A: mFOLFOX6 (standard) + surgery
- mFOLFOX6 (2 weekly cycle):
Oxaliplatin 85 mg/m² iv D1,
Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) D1,
5-FU 400 mg/m² bolus D1 and then 5-FU 2400 mg/m² given as a continuous infusion over 46h.

Study burden and risks

- intake consult
- reading patient information
- if applicable adding targeted antibodies to standard chemotherapy
- if applicable site effects as mentioned

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

- Histologically proven CRC with 1 to 8 metachronous or synchronous liver metastases considered to be completely resectable. (Defined in section 5.5).
- Primary tumor (or liver metastasis) of CRC must be KRAS status *wild type*.
- Patients must have undergone complete resection (R0) of the primary tumor at least 4 weeks before randomization. Or for patients with synchronous metastases the primary tumor can be resected (R0) at the same time as the liver metastases if: the patient has a non-obstructive primary tumor and is able to receive preoperative chemotherapy (3-4 months) before surgery.
- Measurable hepatic disease by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).
- No evidence of extra-hepatic metastasis (of CRC).
- Patients must be 18 years old or older.
- A World Health Organization (WHO) performance status of 0 or 1.
- No previous chemotherapy for metastatic disease or surgical treatment (e.g. surgical resection or radiofrequency ablation) for liver metastasis. Radiotherapy alone is allowed if given pre or post protocol treatment.
- Previous adjuvant chemotherapy for primary CRC is allowed if completed at least 12 months before inclusion in this study.
- No major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to randomization.
- All the following tests should be done within 4 weeks prior to randomization:
- Absolute neutrophil count >= 1.5 x 109/L, platelets >= 100 x 109/L, hemoglobin >= 9 g/dL and white blood cell count (WBC) >= 3 x 109/L.
- Serum creatinine <= 1.5 times the upper limit of normal (ULN) (to exclude severe renal impairment); no significant proteinuria (urine protein < 1g/24 hours urine collection) OR urine protein/creatinine ratio < 1.0 OR 1+ proteinuria on urine dipstick.
- Absence of major hepatic insufficiency (bilirubin <= 1.5 x ULN and aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) <= 5 x ULN).
- Magnesium >= lower limit of normal (LLN)
- Patients with a buffer range from the normal values of +/- 5% for

hematology and +/- 10% for biochemistry are acceptable. This will not apply for Renal Function, including Creatinine.
- No previous exposure to Epidermal Growth Factor Receptor (EGFR) or Vascular Endothelial Growth Factor Receptor (VEGF/VEGFR) targeting therapy within the last 12 months.
- No regular use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).
- No bleeding diathesis (e.g. hemoptysis of >= 1/2 teaspoon or 2.5mL), coagulopathy, or need for administration of full-dose anti-coagulant(s).
- Absence of peripheral neuropathy > grade 1 (Common Terminology Criteria for Adverse Events, v4.0) serious wound complications, ulcers, or bone fractures.
- No clinically significant cardiovascular disease, including: uncontrolled hypertension, New York Heart Association (NYHA) class II-IV heart failure, myocardial infarction or unstable angina pectoris, cerebrovascular accident or transient ischemic attack within the past 12 months, peripheral vascular disease >= grade 2, serious cardiac arrhythmia requiring medication and other clinically significant cardiovascular disease.
-Absence of symptomatic diverticulitis or active or uncontrolled gastroduodenal ulceration.
- No history or evidence of interstitial lung disease (e.g. pneumonitis, pulmonary fibrosis)
- Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 14 days prior to the first dose of study treatment.
- Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 6 months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.
- Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 6 months after the last study treatment.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
- No significant disease that, in the investigator*s opinion, would exclude the patient from the study. Including known allergy or any other adverse reaction to any of the study drugs (including any of the excipients) or to any related compound, including hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanized antibodies.
- No participation in another clinical study (except sub studies of this protocol) within the 30 days before randomization and during this study.
- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

Exclusion criteria

not resectable liver metastases
extra hepatic disease

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-01-2015
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eloxatin
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	5-fluorouracil
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-01-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-06-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-06-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2010-019238-29-NL
ClinicalTrials.gov	NCT01508000
CCMO	NL41328.031.13