Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone: a multicentre, open-label, parallel-group, phase II-III, randomised superiority study (CAIRO6).

Published: 14-09-2016
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-518570-13-00 check the CTIS register for the current data. Objectives of the phase II study (80 patients) are to explore the feasibility of accrual, the feasibility, safety, and tolerance of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Peritoneal and retroperitoneal conditions
Study type	Interventional

Summary

ID

NL-OMON55637

Source
ToetsingOnline

Brief title
CAIRO6

Condition

- Peritoneal and retroperitoneal conditions
- Gastrointestinal neoplasms malignant and unspecified
- Gastrointestinal therapeutic procedures

Synonym
Peritoneal metastases of colorectal cancer; Colon cancer with metastases in the peritoneum

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: KWF Kankerbestrijding,Catharina Onderzoeksfonds,Hoffman-La Roche

Intervention

Keyword: Colorectal neoplasms, Induction chemotherapy, Molecular targeted therapy, Peritoneal neoplasms

Outcome measures

Primary outcome

Endpoints of the phase II study are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological/histological response of colorectal PM to neoadjuvant systemic therapy. The primary endpoint of the phase III study is 3-year overall survival, which is hypothesised to be 50% in the control arm and 65% in the experimental arm, thereby requiring 358 patients (179 in each arm).

Secondary outcome

Secondary endpoints are surgical characteristics, grade >=3 postoperative morbidity, progression-free survival, disease-free survival, health-related quality of life, costs, major systemic therapy related toxicity, and objective radiological and histological response rates of colorectal PM to neoadjuvant systemic therapy.

Study description

Background summary

Cytoreductive surgery with HIPEC (CRS-HIPEC) is a curative intent treatment for patients with isolated resectable colorectal peritoneal metastases (PM). Upfront CRS-HIPEC alone is the standard treatment in the Netherlands. The addition of neoadjuvant and adjuvant systemic therapy (together: perioperative systemic therapy) to CRS-HIPEC could have benefits and drawbacks. Potential benefits are eradication of systemic micrometastases, preoperative intraperitoneal tumour downstaging, elimination of post-surgical residual cancer cells, and improved patient selection for CRS-HIPEC. Potential drawbacks are preoperative disease progression and secondary unresectability for CRS-HIPEC, systemic therapy related toxicity, increased postoperative morbidity, decreased quality of life, and higher costs. Currently, there is a complete lack of randomised studies that prospectively compare the oncological efficacy of perioperative systemic therapy and CRS-HIPEC with upfront CRS-HIPEC alone. Notwithstanding this lack of evidence, perioperative systemic therapy is widely administered to patients with isolated resectable colorectal PM. However, administration and timing of perioperative systemic therapy vary substantially between countries, hospitals, and guidelines. More importantly, it remains unknown whether perioperative systemic therapy has an intention-to-treat benefit in this setting. Therefore, this study randomises patients with isolated resectable colorectal PM to receive either perioperative systemic therapy (experimental arm) or upfront CRS-HIPEC alone (control arm).

Study objective

This study has been transitioned to CTIS with ID 2024-518570-13-00 check the CTIS register for the current data.

Objectives of the phase II study (80 patients) are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological and histological response of colorectal PM to neoadjuvant systemic therapy. The primary objective of the phase III study (an additional 278 patients) is to compare survival outcomes between both arms. Secondary objectives are to compare surgical characteristics, major postoperative morbidity, health-related quality of life, and costs between both arms. Other objectives are to assess major systemic therapy related toxicity and the objective radiological and histological response of colorectal PM to neoadjuvant systemic therapy.

Study design

A multicentre, open-label, parallel-group, phase II-III, superiority study that randomises eligible patients in a 1:1 ratio.

Intervention

At the discretion of the treating medical oncologist, perioperative systemic therapy consists of either four 3-weekly neoadjuvant and adjuvant cycles of capecitabine with oxaliplatin (CAPOX), six 2-weekly neoadjuvant and adjuvant cycles of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX), or six 2-weekly neoadjuvant cycles of 5-fluorouracil/leucovorin with irinotecan (FOLFIRI) followed by either four 3-weekly (capecitabine) or six 2-weekly (5-fluorouracil/leucovorin) adjuvant cycles of fluoropyrimidine monotherapy. Bevacizumab is added to the first three (CAPOX) or four (FOLFOX/FOLFIRI) neoadjuvant cycles.

Study burden and risks

It is hypothesised that perioperative systemic therapy and CRS-HIPEC (experimental arm) significantly improve the overall survival of patients with isolated resectable colorectal PM compared to the current standard treatment with upfront CRS-HIPEC alone (control arm). This potential overall survival benefit should be weighed against the burden and risks of the experimental arm. The most important potential burden/risks are: additional hospital visits for the perioperative systemic therapy, preoperative disease progression and secondary unresectability for CRS-HIPEC, increased postoperative complications after CRS-HIPEC, toxicity of perioperative systemic therapy, and an intensified and prolonged initial treatment that could decrease health-related quality of life. The investigators feel that the potential overall survival benefit of the experimental arm outweighs the burden and risks of participation. Patients in both arms are given to possibility to give separate permission for receiving questionnaires (costs, health-related quality of life) and for participation in blood and tissue collection for translational research.

Contacts

Public
Catharina-ziekenhuis

Michelangelolaan 2
Eindhoven 5623 EJ
NL
Scientific
Catharina-ziekenhuis

Michelangelolaan 2
Eindhoven 5623 EJ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligible patients are adults who have:
* a World Health Organisation (WHO) performance status of <=1;
* histological or cytological proof of PM of a non-appendiceal colorectal adenocarcinoma with <=50% of the tumour cells being signet ring cells;
* resectable disease determined by abdominal computed tomography (CT) and a diagnostic laparoscopy/laparotomy;
* no evidence of systemic colorectal metastases within three months prior to enrolment;
* no systemic therapy for colorectal cancer within six months prior to enrolment;
* no contraindications for CRS-HIPEC;
* no previous CRS-HIPEC;
* no concurrent malignancies that interfere with the planned study treatment or the prognosis of resected colorectal PM.

Exclusion criteria

Patients are excluded in case of any comorbidity or condition that prevents safe administration of the planned perioperative systemic therapy, determined by the treating medical oncologist, e.g.:
* Inadequate bone marrow, renal, or liver functions (e.g. haemoglobin <6.0 mmol/L, neutrophils <1.5 x 109/L, platelets <100 x 109/L, serum creatinine >1.5 x ULN, creatinine clearance <30 ml/min, bilirubin >2 x ULN, serum liver transaminases >5 x ULN);
* Previous intolerance of fluoropyrimidines or both oxaliplatin and irinotecan;
* Dehydropyrimidine dehydrogenase deficiency;
* Serious active infections;

* Severe diarrhoea;
* Stomatitis or ulceration in the mouth or gastrointestinal tract;
* Recent major cardiovascular events;
* Unstable or uncompensated respiratory or cardiac disease;
* Bleeding diathesis or coagulopathy;
* Pregnancy or lactation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-06-2017
Enrollment:	298
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	5-fu
Generic name:	5-fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Folinic acid
Generic name:	Leucovorin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Oxaliplatin
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	Capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-09-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2017

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-04-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-04-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	17-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-11-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
EU-CTR	CTIS2024-518570-13-00
EudraCT	EUCTR2016-001865-99-NL
ISRCTN	ISRCTN15977568;NCT02758951;NTR6301
CCMO	NL57644.100.16